Medical Management and Surveillance in Marfan Syndrome and Loeys-Dietz Syndrome

Alan C. Braverman, MD

Alumni Endowed Professor in Cardiovascular Diseases
Director, Marfan Syndrome and Aortopathy Clinic
Director, Neidorff Aortopathy and Master Clinician in Cardiology Fellowship Program
Section Head, General Cardiology
Washington University in St. Louis School of Medicine

WashU

Vascular Genetics Symposium

Oregon Health Sciences University
Portland, OR October 3, 2025

Barnes-Jewish Hospital
BJC HealthCare

I have no disclosures.

Components of “Medical” Management in Marfan and Loeys-Dietz

- Diagnosis
  - Family/Cascade Screening
- Lifestyle/behavioral
  - exercise/physical exertion
  - healthy lifestyle (diet, movement, avoid tobacco/illicit drugs, alcohol excess)
  - BP, cholesterol, blood sugar, obesity
- Family Planning/Contraception/Pregnancy
- Education
  - care, advocacy, action plan (emergency/aortic dissection)
- **Imaging**
  - echocardiogram, CTA/MRA
- **Medication/Pharmacotherapy**

Pharmacotherapy in Marfan syndrome

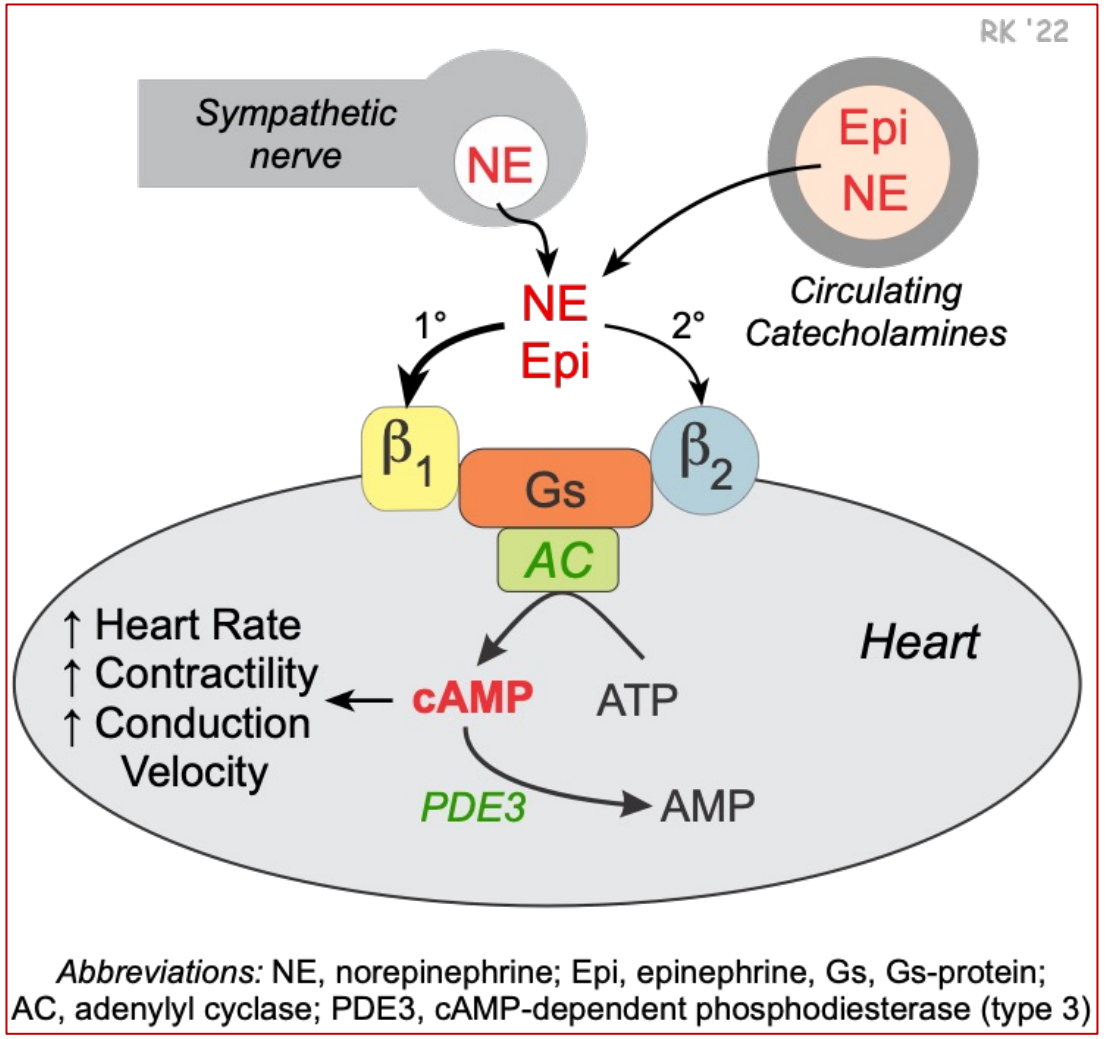
Medical Therapy: Beta Blocker Therapy in the Marfan Syndrome

Beta Blockers: Beta-Adrenergic Receptor Antagonists

1. Decrease inotropic state of heart

2. Decrease impact force of ejected blood on the aortic wall

3. Decrease blood pressure and heart rate



Abbreviations: NE, norepinephrine; Epi, epinephrine, Gs, Gs-protein; AC, adenylyl cyclase; PDE3, cAMP-dependent phosphodiesterase (type 3)

https://cvpharmacology.com/cardioinhibitory/beta-blockers

Beta Blockers and the Marfan Syndrome

1971 Halpern et al suggested Beta blockade might reduce the risk of aortic dissection in the Marfan syndrome [1,2]

- In patients with malignant hypertension, reducing BP to normal, but not reducing the rate of rise of BP (dP/dt) did not prevent risk of dissection [3]

- Beta blockers effective in the long-term management of aortic dissection [4]

1. Shores J. N Engl J Med 1994;330:1335-41
2. Halpern BL. Johns Hopkins Med J 1971:129:123-9
3. Beaven DW. BMJ 1956;1:77-80
4. Wheat MW. J Thorac Cardiovasc Surg 1965:50:364-73.

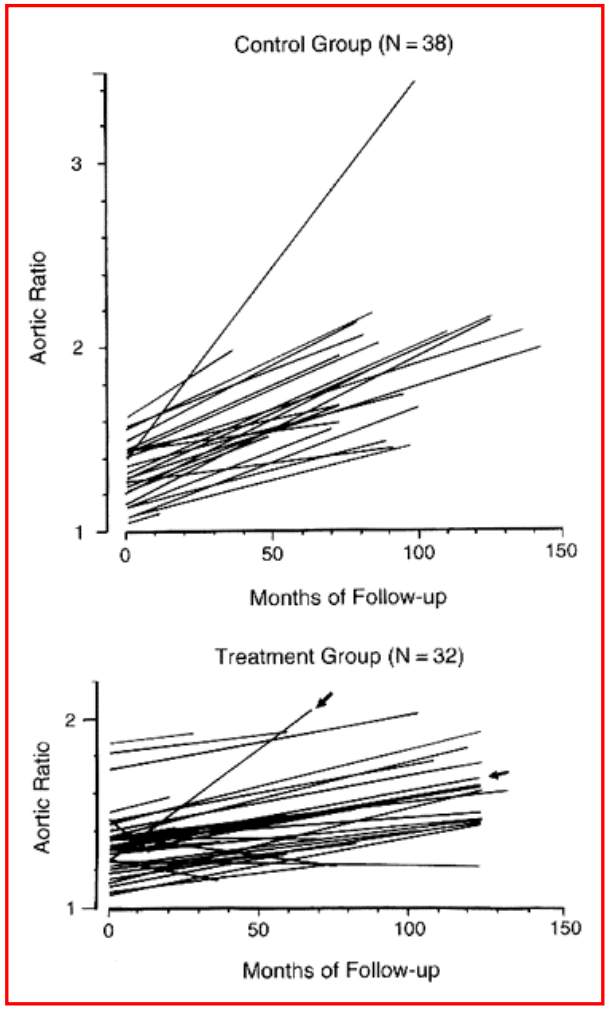
Beta Blockers and the Marfan Syndrome

- Turkeys prone to spontaneous dissection/rupture had improved survival when propranolol was added to their feed [5]

- Models of aortic dissection suggested reducing dP/dt was more protective than reducing mean BP [6]

5. Simpson CF. Toxicol Appl Pharmacol 1976;38:169-75
6. Prokop EK. Circ Res 1970; 27:121-7.

Beta Blocker Therapy in Marfan Syndrome



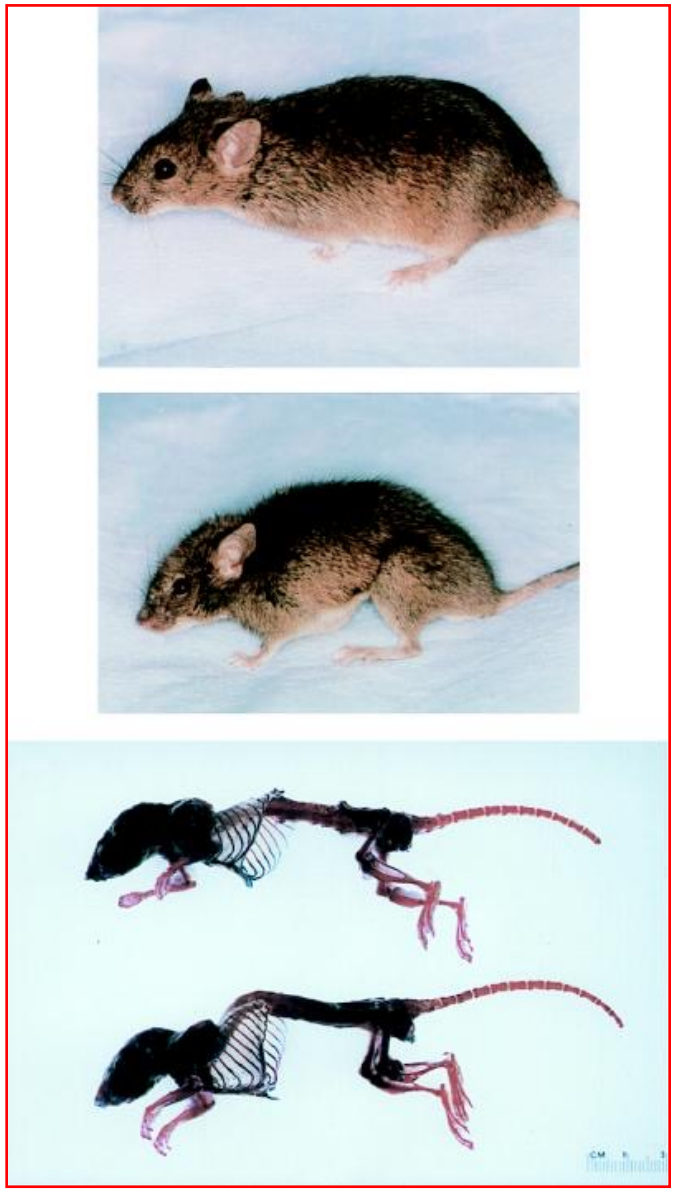
Randomized, controlled trial of propranolol in Marfan syndrome and mild to moderate aortic dilatation.

2 Beneficial Effects of Beta Blockers

- Decreased rate of aortic root enlargement
- Fewer patients developed aortic regurgitation or dissection

Shores et al. New Engl J Med. 1994;330:1335-41

Marfan Syndrome: Research into Novel Therapies



Mouse heterozygous for missense mutaton in fibrillin
Courtesy of Dr. F. Ramirez

- Fibrillin-1 and microfibrils regulate the TGF-β family of growth factors (cytokines) that influence many aspects of cellular performance (differentiation, proliferation, protein production)

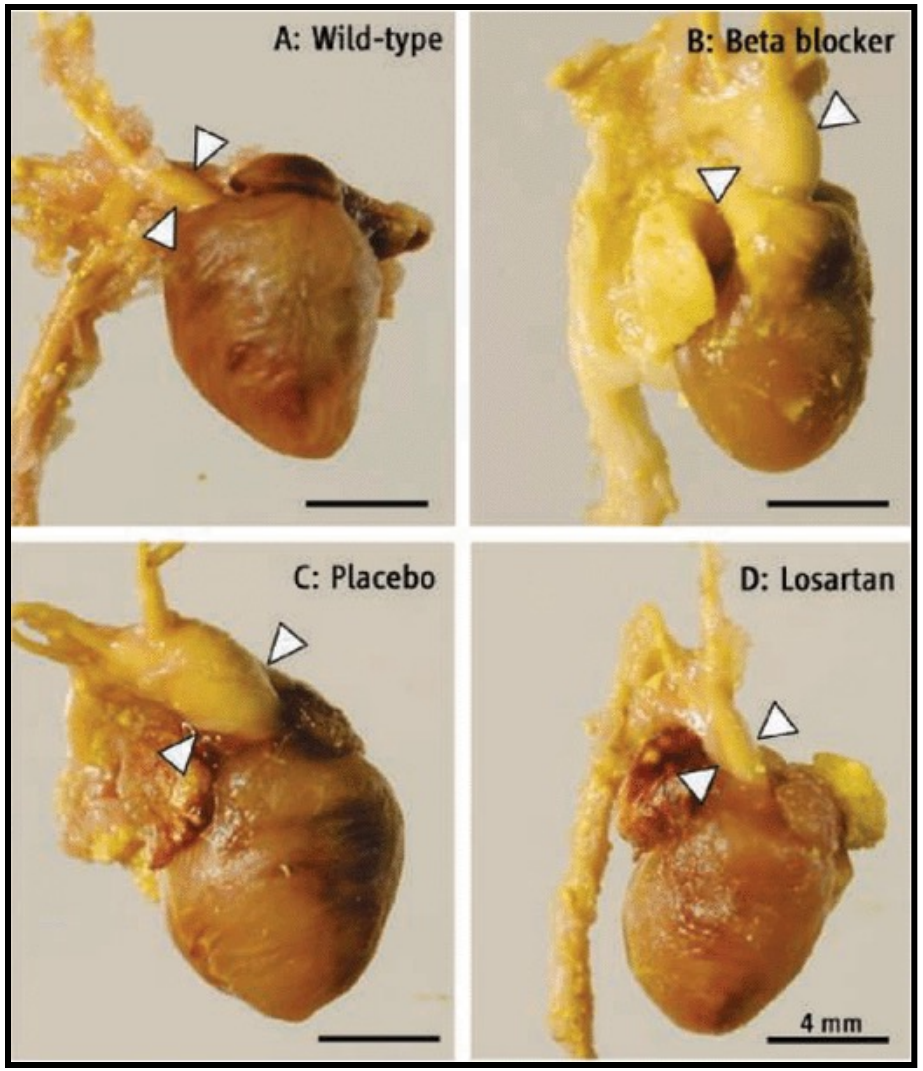
- **Mouse model** of Marfan Syndrome: Deficiency of fibrillin-1 microfibrils results in excessive TGF-β activation and signaling in tissues altered by Marfan syndrome, including the aortic wall.

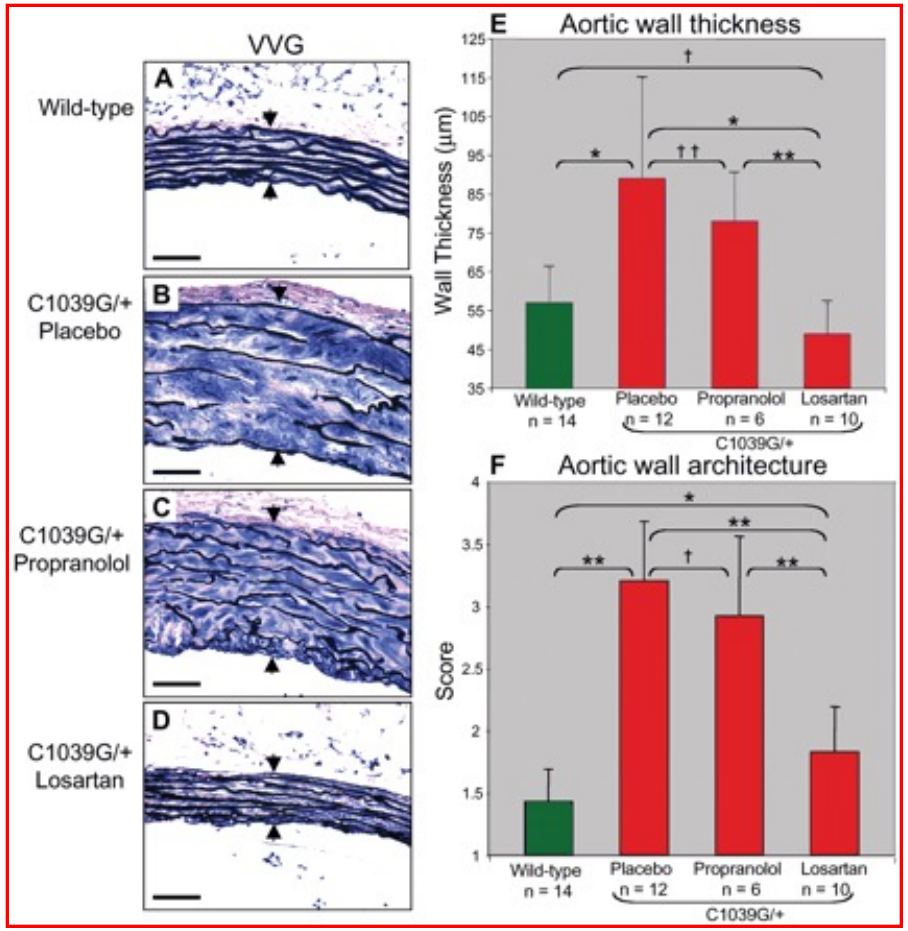
Milewicz DM et al. Circulation 2005;111:e150-e157.

Habashi JP et al. Science. 2006;312(5770):117-121.

Losartan, an Angiotensin-1 Receptor Antagonist, Prevents Aortic Aneurysm in a Mouse Model of Marfan Syndrome

Habashi JP et al. Science 2006;312:117-121

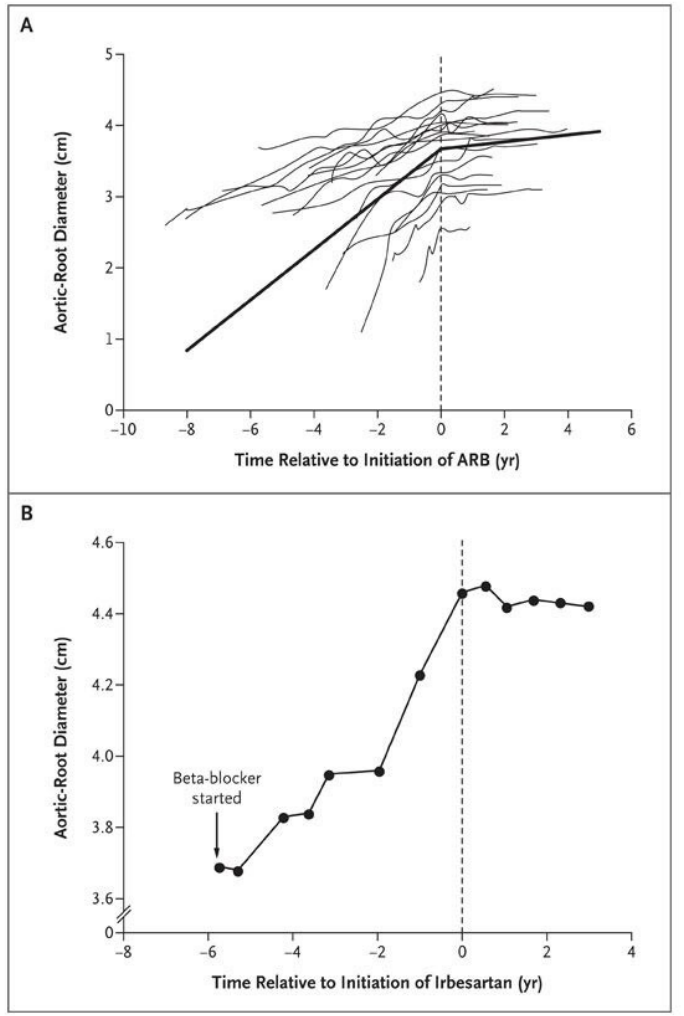




ARB Therapy in Marfan Syndrome

Brooke et al. NEJM 2008;358:2787

- 17 patients aged 14 months to 16 years who had received ARB therapy for >1 year.
- These patients had severe aortic enlargement (mean z-score of 7.2 at time of ARB therapy).
- Patients on ARB therapy had significant decrease in the rate of change of aortic root diameter (3.5 mm/yr vs. 0.5 mm/yr).



Change in Aortic-Root Diameter Standardized According to the Time of Initiation of Therapy with an Angiotensin II–Receptor Blocker (ARB).

ORIGINAL ARTICLE

Atenolol versus Losartan in Children and Young Adults with Marfan's Syndrome

Ronald V. Lacro, M.D., Harry C. Dietz, M.D., Lynn A. Sleeper, Sc.D., Anji T. Yetman, M.D., Timothy J. Bradley, M.B., Ch.B., Steven D. Colan, M.D., Gail D. Pearson, M.D., Sc.D., E. Seda Selamet Tierney, M.D., Jami C. Levine, M.D., Andrew M. Atz, M.D., D. Woodrow Benson, M.D., Ph.D., Alan C. Braverman, M.D., et al., for the Pediatric Heart Network Investigators*

N Engl J Med 2014;371:2061-71.

- 608 patients with Marfan syndrome from 21 centers, aged 6 months to 25 years (mean 11.5 ± 6 yrs) with aortic z-score >3.0 were randomized to either:

Atenolol (up to 4 mg/kg) [titrated to decrease mean HR >20%]

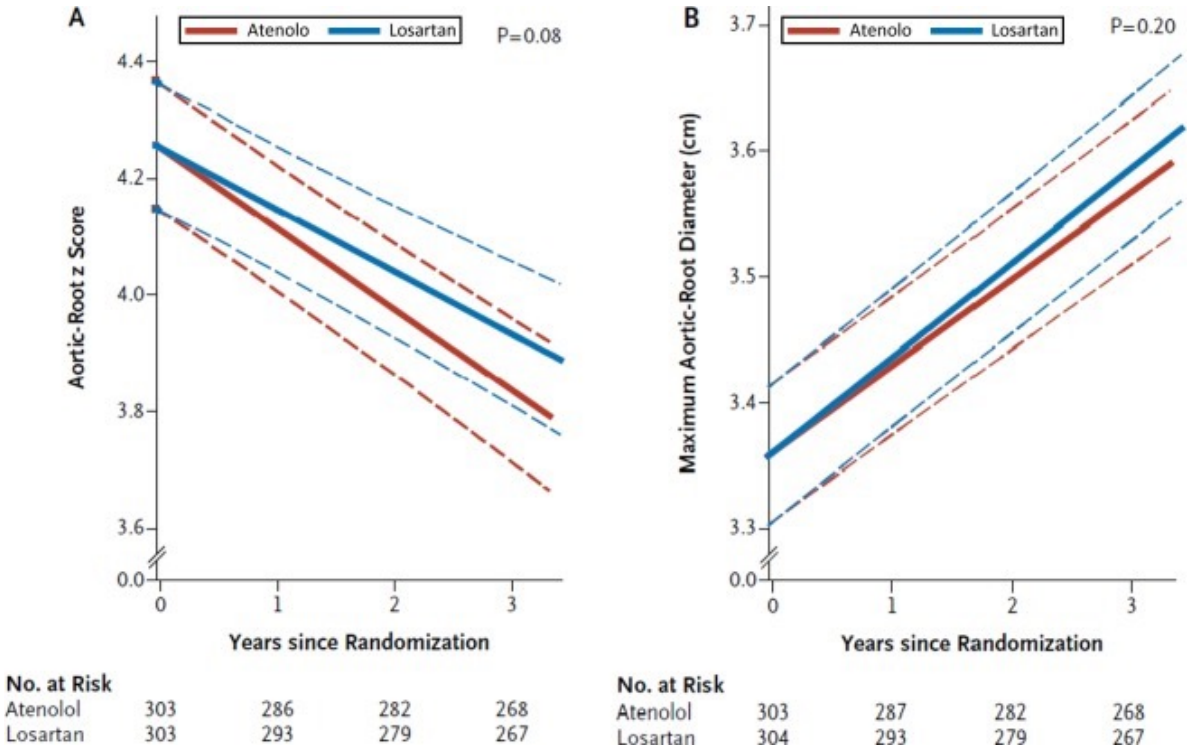
[average dose 2.7 mg/kg or 151 ± 75 mg/d in young adults]

or

Losartan (up to 1.4 mg/kg)

[average dose 1.3 mg/kg or 85 ± 14 mg/d in young adults]

Changes in aortic root z-score and aortic root diameter according to treatment group



- No difference in rate of change of aortic root z-score between the atenolol group and the losartan group (-0.139 and -0.107), respectively.

- Both slopes were significantly less than zero, indicating a decrease in aortic root dilatation relative to BSA with either treatment.

Outcomes:

The 3-year rates of aortic root surgery, aortic dissection, death, and a composite of these events did not differ significantly between the two treatment groups.

- Marfan Sartan: French Marfan Trial. Milleron O et al. Eur Heart J. 2015;36:2160-6.
- Spanish Marfan Trial. Forteza A et al. Eur Heart J. 2016;37:978-85.

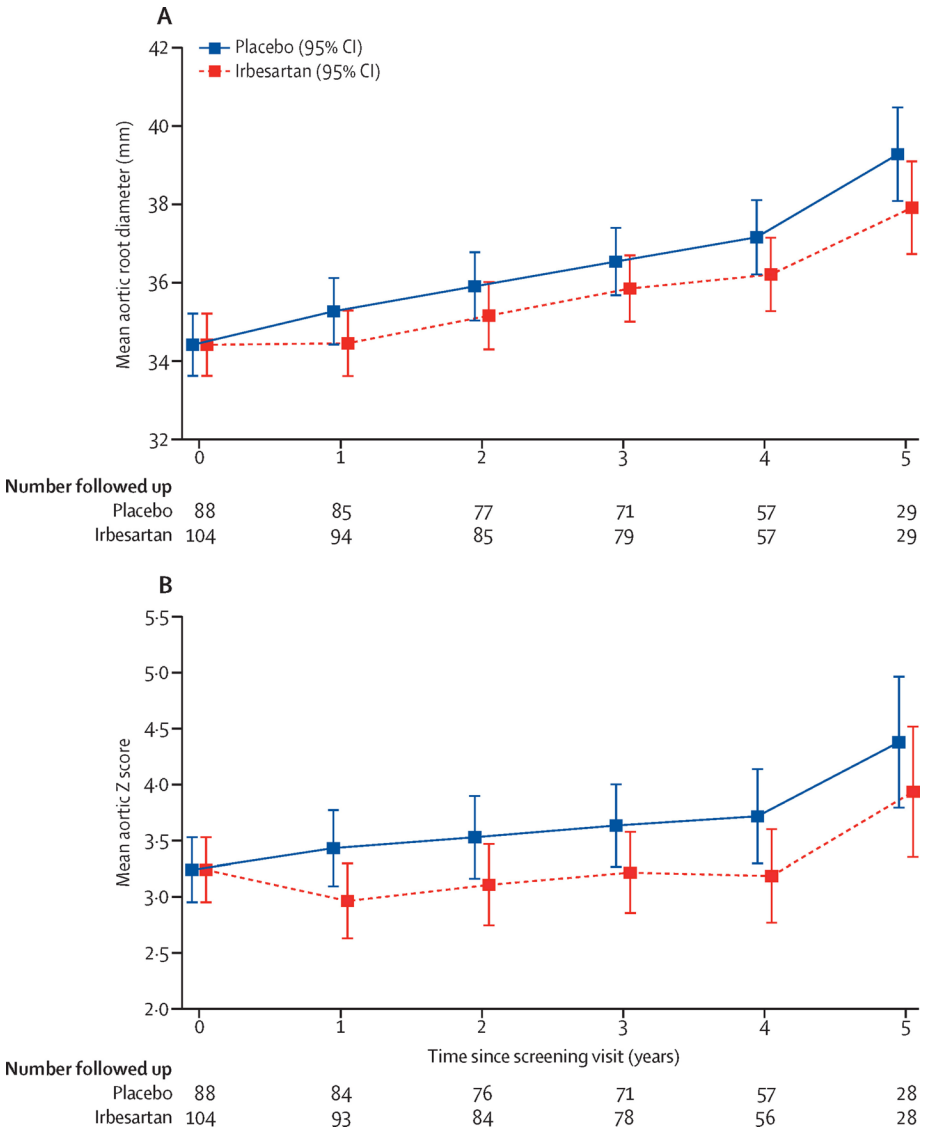
No differences in aortic root growth comparing beta blocker to losartan over a 3-year study period.

AIMS Trial (UK)

Mullen M et al. Lancet 2019;394:2263-70

Irbesartan in Marfan Syndrome

- Irbesartan use associated with a lower rate of aortic growth rate by 0.22 mm/year compared to placebo.
- *56% of patients also treated with a beta blocker



Angiotensin receptor blockers and β blockers in Marfan syndrome: an individual patient data meta-analysis of randomised trials

Alex Pitcher, Enti Spata, Jonathan Emberson, Kelly Davies, Heather Halls, Lisa Holland, Kate Wilson, Christina Reith, Anne H Child, Tim Clayton, Matthew Dodd, Marcus Flather, Xu Yu Jin, George Sandor, Maarten Groenink, Barbara Mulder, Julie De Backer, Arturo Evangelista, Alberto Forteza, Gisela Teixido-Turà, Catherine Boileau, Guillaume Jondeau, Olivier Milleron, Ronald V Lacro, Lynn A Sleeper, Hsin-Hui Chiu, Mei-Hwan Wu, Stefan Neubauer, Hugh Watkins, Hal Dietz, Colin Baigent, on behalf of The Marfan Treatment Trialists' Collaboration

- In people with Marfan syndrome and no previous aortic surgery, ARBs reduced the rate of increase of the aortic root Z score by about one half, including among those taking a β blocker.
- The effects of β blockers were similar to those of ARBs.
- Assuming additivity, combination therapy with both ARBs and β blockers from the time of diagnosis would provide even greater reductions in the rate of aortic enlargement than either treatment alone, which, if maintained over a number of years, would be expected to lead to a delay in the need for aortic surgery

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

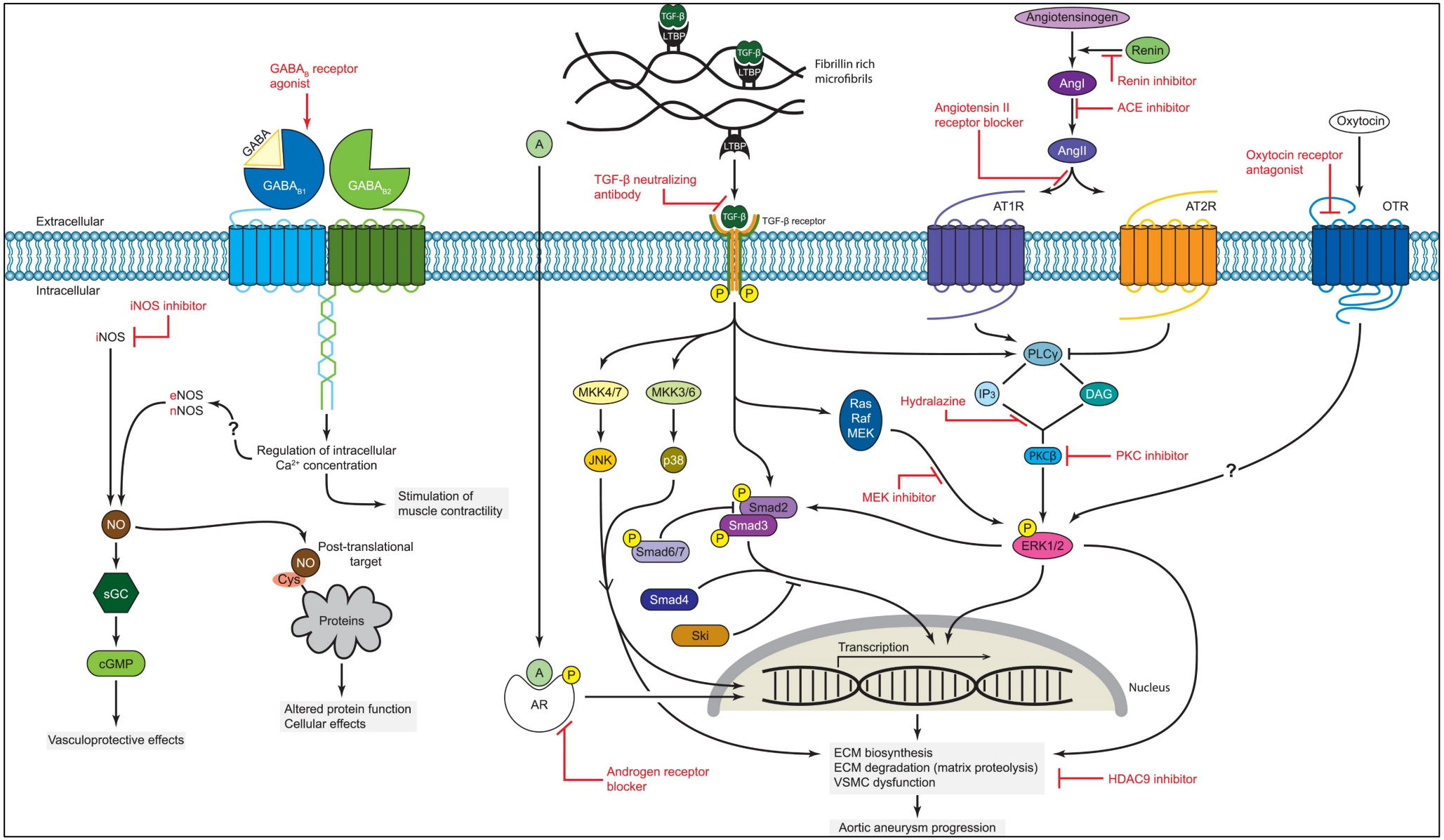
Recommendations for Medical Therapy in Marfan Syndrome

COR	LOE	RECOMMENDATIONS
1	A	In patients with Marfan syndrome, treatment with either a beta blocker or an angiotensin receptor blocker (ARB) in maximally tolerated doses is recommended (unless contraindicated) to reduce the rate of aortic dilation.[1,2]
2a	C-LD	In patients with Marfan syndrome, the use of both a beta blocker and an ARB in maximally tolerated doses is reasonable (unless contraindicated) to reduce the rate of aortic dilation.[3,4,11]

Isselbacher EM, Preventza O, Hamilton Black Iii J, Augoustides JG, Beck AW, Bolen MA, Braverman AC, et al. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease. J Am Coll Cardiol. 2022;80:e223-e393.

Proposed molecular mechanisms involved in MFS pathology and potential treatment targets.

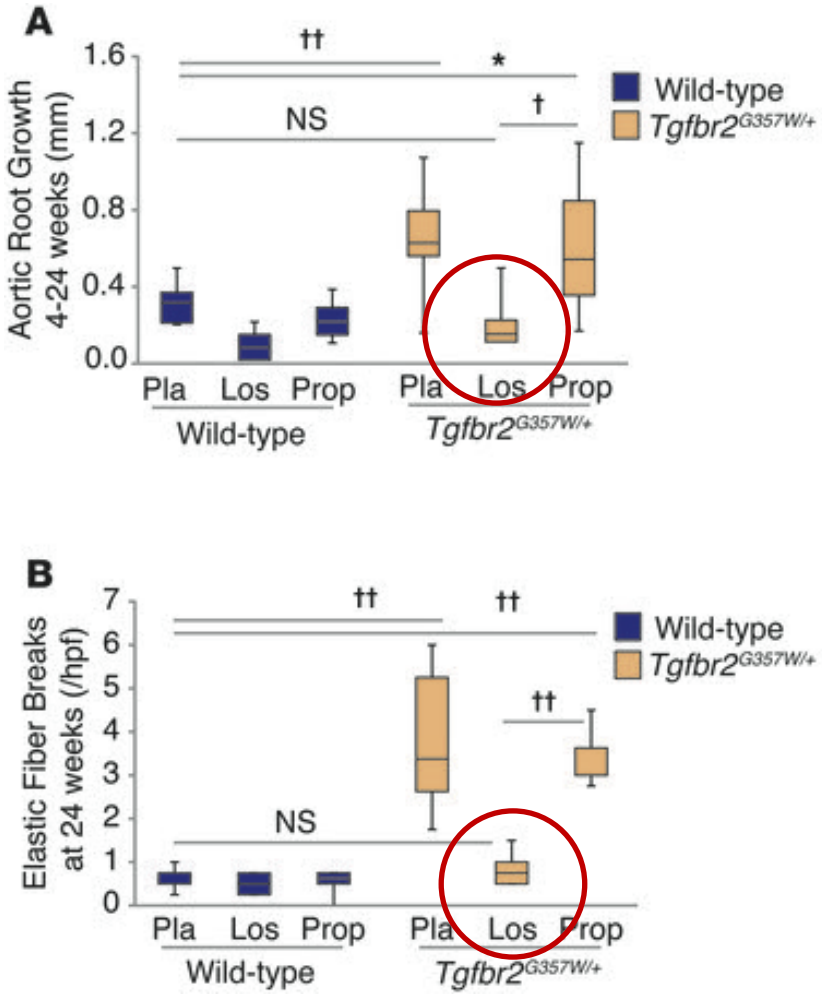
Deleeuw et al. J Exp Pharmacol 2021

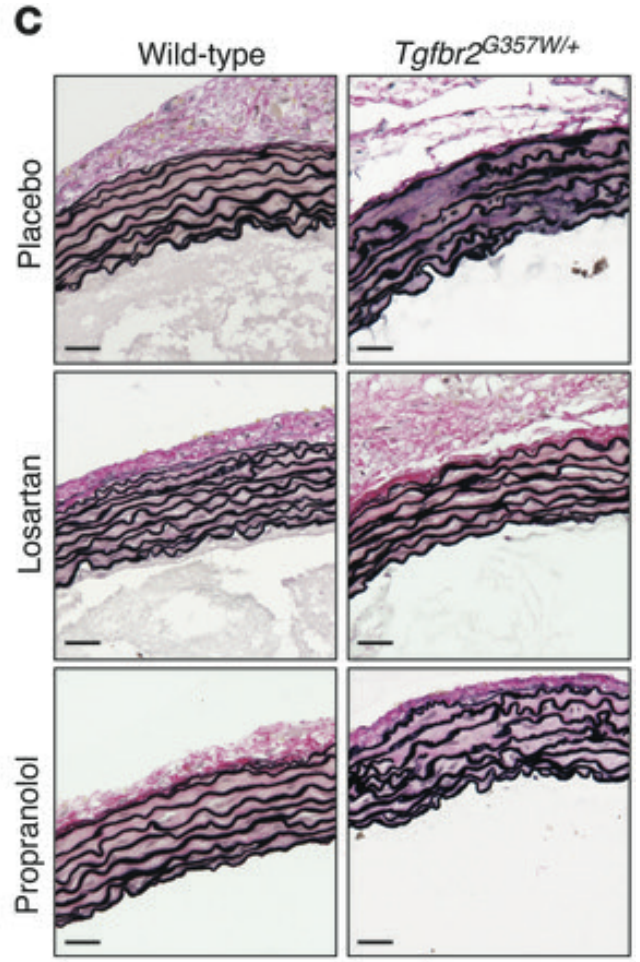


Pharmacotherapy in Loeys-Dietz Syndrome

Angiotensin II–dependent TGF-β signaling contributes to Loeys-Dietz syndrome vascular pathogenesis

Gallo GM…..Dietz HC. J Clin Invest DOI: 10.1172/JCI69666





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

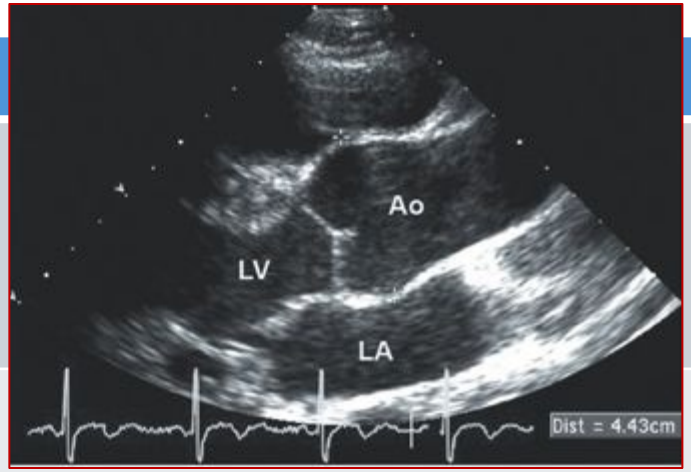
Recommendations for Medical Therapy in Loeys-Dietz Syndrome

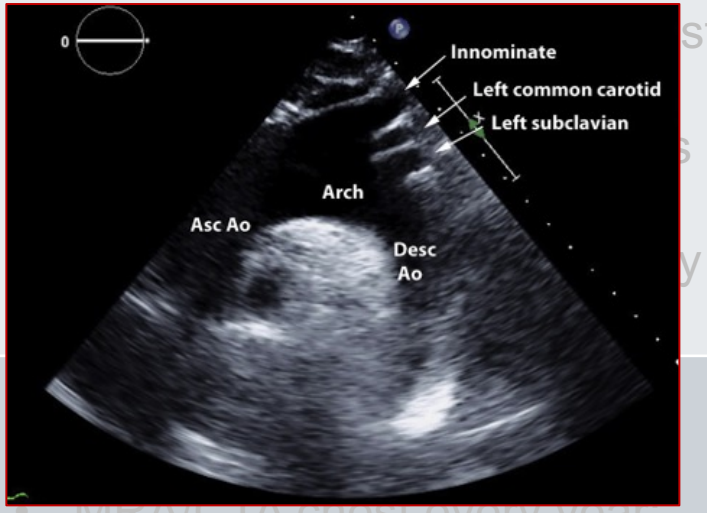
COR	LOE	RECOMMENDATIONS
2a	C-EO	In patients with Loeys-Dietz syndrome, treatment with a beta blocker or an angiotensin receptor blocker (ARB) or both, in maximally tolerated doses is reasonable (unless contraindicated).

Isselbacher EM, Preventza O, Hamilton Black Iii J, Augoustides JG, Beck AW, Bolen MA, Braverman AC, et al. 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease. J Am Coll Cardiol. 2022;80:e223-e393.

Imaging Surveillance in Marfan Syndrome and Loeys-Dietz Syndrome

	Marfan Syndrome
Initial imaging	• **Echocardiogram** • **Consideration of chest CTA/MRA**
Subsequent imaging	• **Annual echocardiogram**
Postoperative imaging	• **Annual echocardiogram** • **MRA/CTA every year; if stable, image at regular intervals (2-years)**





Imaging Surveillance in Marfan Syndrome and Loeys-Dietz Syndrome

	Marfan Syndrome	Loeys-Dietz Syndrome
Initial imaging	• Echocardiogram • Consideration of chest CTA/MRA	• **Echocardiogram** • **CTA or MRA head to pelvis**
Subsequent imaging	• Annual echocardiogram	• **Annual echocardiogram** • **Consideration of MRA/CTA chest** • **MRA/CTA C/A/P every 2 years** • **MRA/CTA head and neck every 2-3 years**
Postoperative imaging	• Annual echocardiogram • MRA/CTA every year; if stable, image at regular intervals (2-years)	• **Annual echocardiogram** • **MRA/CTA chest every year; if stable, image MRA/CTA C/A/P every 2 years.**

Importance of Surveillance Imaging in Marfan Syndrome and Loeys-Dietz Syndrome

- Echocardiogram
  - Aortic valve function (AR after VSRR; AVR function)
  - Mitral valve function (MVP, MR, MAD)
  - LVEF, cardiomyopathy
  - Other valve function

- MRA/CTA
  - Arterial tortuosity
  - Coronary button aneurysms
  - Ascending aortic, arch, descending aorta dilation
  - Graft pseudoaneurysms (coronary button, distal anastomosis)

  - Branch vessel aneurysms
  - Branch vessel dissection
  - Distal aortic dilation; iliac artery aneurysm

After aortic dissection: progressive aortic dilation/aneurysm

Circulation
Volume 146, Issue 2, 12 July 2022; Pages 142-143

RESEARCH LETTER

Frequency of Screening-Detected Intracranial Aneurysms in Patients With Loeys-Dietz Syndrome

Anna L. Huguenard, MD, Gabrielle W. Johnson, BA, Joshua W. Osbun, MD, Ralph G. Dacey, MD, and Alan C. Braverman, MD

Table. **ICAs in LDS**

Genetic variant	Patients, n	Distinct families, n	Probands evaluated, n	Patients with >1 ICA, n (%)	Patients with >2 ICAs, n (%)	ICAs, n	Saccular ICAs, n	Fusiform ICAs, n	Average ICA diameter (SD), mm
Overall	80	58	47	18/80 (22.5)	6/80 (7.5)	28	20	8	3.4 (2.3)
TGFBR1	21	15	9	4/21 (19.0)	2/21 (9.5)	7	4	3	3.0 (1.2)
TGFBR2	24	18	16	5/24 (20.8)	2/24 (8.3)	9	6	3	3.7 (2.8)
SMAD3	13	9	7	6/13 (46.2)	1/13 (7.7)	8	7	1	3.1 (1.5)
TGFB2	15	9	8	2/15 (13.3)	1/15 (6.7)	3	2	1	4.7 (4.6)
TGFB3	7	7	7	1/7 (14.3)	0/7 (0)	1	1	0	3.0 (N/A)

JNS

CLINICAL ARTICLE

J Neurosurg 140:1381–1388, 2024

Natural history and growth rate of intracranial aneurysms in Loeys-Dietz syndrome: implications for treatment

Anna L. Huguenard, MD,[1] Gabrielle W. Johnson, MD, MSCI,[1] Joshua W. Osbun, MD,[1] Ralph G. Dacey Jr., MD,[1] and Alan C. Braverman, MD[2]

[1]Department of Neurosurgery, Washington University in St. Louis, Missouri; and [2]Department of Medicine, Cardiovascular Division, Washington University in St. Louis, Missouri

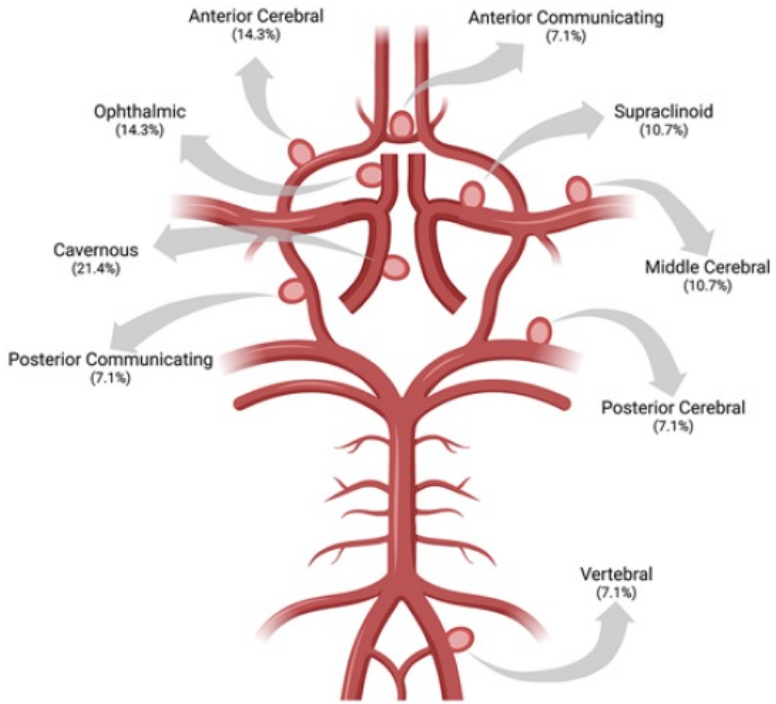


FIG. 1. Distribution of anatomical locations where intracranial aneurysms were identified. Figure is available in color online only.

TABLE 2. Locations of ICAs in LDS patients

Vessel Location of Aneurysm	Aneurysms	Mean Aneurysm Diameter (SD), mm
Overall	28	3.2 (1.8)
Anterior circulation	22 (78.6)	3.2 (1.4)
Cavernous	6 (21.4)	4.3 (1.7)
Ophthalmic	4 (14.3)	3.5 (0.5)
Anterior cerebral	4 (14.3)	2.3 (1.0)
Middle cerebral	3 (10.7)	2.2 (0.6)
Supraclinoid internal carotid	3 (10.7)	3.4 (1.2)
Anterior communicating	2 (7.1)	2.0 (0)
Posterior circulation	6 (21.4)	3.6 (2.9)
Posterior communicating	2 (7.1)	2.5 (0.5)
Posterior cerebral	2 (7.1)	2.0 (0)
Vertebral	2 (7.1)	6.2 (3.9)

Values are shown as number or number (%) unless indicated otherwise.

TABLE 3. Rate of growth of ICAs in patients with LDS

	Growth Rate					
	No Growth Rate Calculated*	0 mm/yr	0.0–0.5 mm/yr	0.5–1.0 mm/yr	>1.0 mm/yr	Mean (SD), mm/yr
Overall (n = 19)	2 (10.5)	6 (31.6)	4 (21.1)	5 (26.3)	2 (10.5)	0.43 (0.53)
TGFBR1 (n = 4)	1 (25.0)	0 (0)	0 (0)	2 (50.0)	1 (25.0)	0.83 (0.38)
TGFBR2 (n = 5)	1 (20.0)	2 (40.0)	1 (20.0)	1 (20.0)	0 (0)	0.22 (0.26)
SMAD3 (n = 7)	0 (0)	3 (42.9)	2 (28.6)	2 (28.6)	0 (0)	0.24 (0.27)
TGFB2 (n = 2)	0 (0)	0 (0)	1 (50.0)	0 (0)	1 (50.0)	1.17 (0.74)
TGFB3 (n = 1)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)

JNS

CLINICAL ARTICLE

J Neurosurg 138:1385–1392, 2023

Relationshi
syndrome a

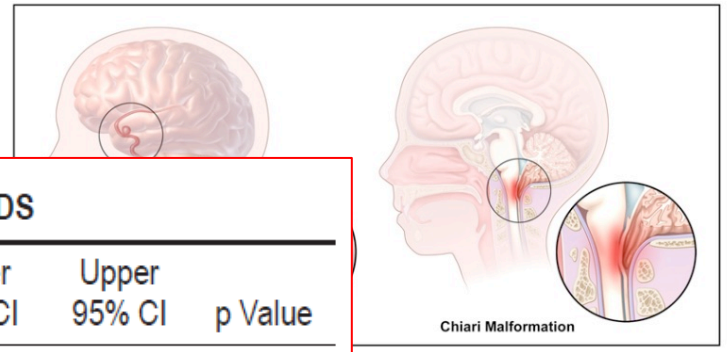
*Anna L. Huguenar
Joshua W. Osbun,

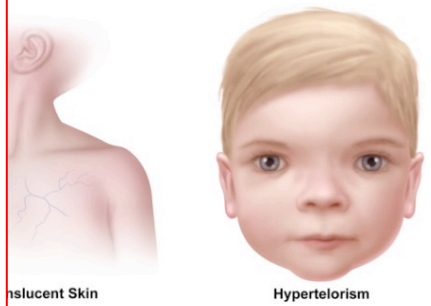
[1]Department of Neurosur
Washington University in

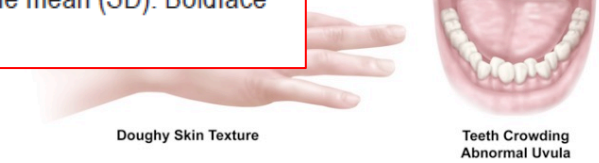
TABLE 5. Assessed craniofacial risk factors for intracranial aneurysms in LDS

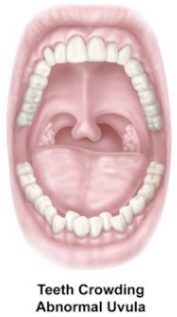
Risk Factor	Patients w/o ICA (n = 63)	Patients w/ ICA (n = 18)	OR	Lower 95% CI	Upper 95% CI	p Value
Craniosynostosis	10 (15.9)	4 (22.2)	1.51	0.41	5.56	0.53
Hypertelorism	26 (41.3)	7 (38.9)	0.88	0.30	2.58	0.82
Abnormal uvula	21 (33.3)	7 (38.9)	1.24	0.42	3.67	0.70
Teeth crowding	15 (23.8)	7 (38.9)	2.15	0.70	6.63	0.18
Doughy skin texture	42 (66.7)	14 (77.8)	1.67	0.49	5.72	0.42
Thin/translucent skin	45 (71.4)	14 (77.8)	1.32	0.38	4.59	0.66
CM-I	2 (3.2)	4 (22.2)	8.71	1.45	52.4	**0.02**
Marfan systemic score	5.74 (3.63)	5.56 (3.45)	0.99	0.85	1.14	0.85
CFI score	1.74 (2.41)	2.06 (2.04)	1.06	0.85	1.32	0.61

Dichotomous variables are reported as number (%), and continuous variables are reported as the mean (SD). Boldface type indicates statistical significance.









Stroke

New online

https://doi.org/

ORIGINAL

Three-

Predic

Syndr

Jin Vivian

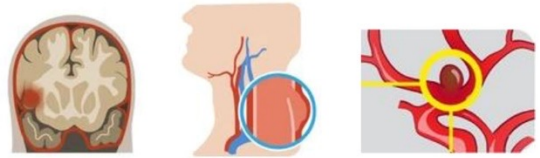
G. Dacey,

American Heart Association.

ery

, Ralph

Participants

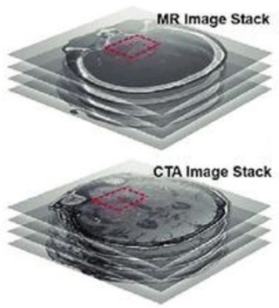


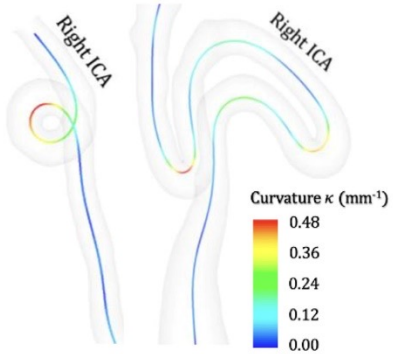
63 Loeys-Dietz Syndrome patients

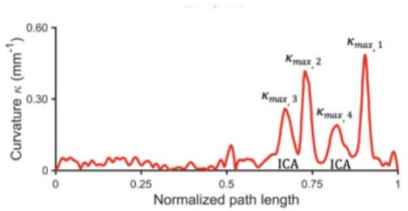
- Follow-up: 8.7 ± 4.1 years
- Adverse neurovascular events during follow-up: 37%
- 5- and 10-year outcomes

Quantification

CTA/MRA → Three-dimensional vessel modeling → Carotid total curvature







$$TAC = \int \kappa(s) ds$$

Results

Higher baseline total curvature

- Higher multiple vessel CA/VA dissection rate
- Higher ischemic stroke and ICH rate
- Higher unruptured IC aneurysm tx rate

Odds ratio of adverse neurovascular event within 5 years: 7.2 (95% CI, 2.0-25.4)

JACC
VOL. 85, NO. 24, 2025

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Characterization of Arterial Aneurysms in Loeys-Dietz Syndrome

Andrew W. Koefoed, BA,[a] Anna L. Huguenard, MD,[b] Gabrielle W. Johnson, MD, MSCI,[a] Elena Deych, MS,[c] Dongchuan Guo, PhD,[d] Dianna M. Milewicz, MD, PhD,[d] Alan C. Braverman, MD[c]

ABSTRACT

BACKGROUND The presence of extra-aortic arterial aneurysms (AAs) is notable in Loeys-Dietz syndrome (LDS) compared with other heritable thoracic aortic diseases (HTADs). However, the characteristics of AAs in LDS are poorly characterized to date.

OBJECTIVES We sought to determine the prevalence, characteristics, and clinical outcomes of AAs in LDS.

METHODS A retrospective cohort study of LDS patients evaluated at Washington University in St Louis School of Medicine/Barnes-Jewish Hospital between 1998 and 2023 was performed. Clinical information, imaging data, and outcomes related to AAs were compiled.

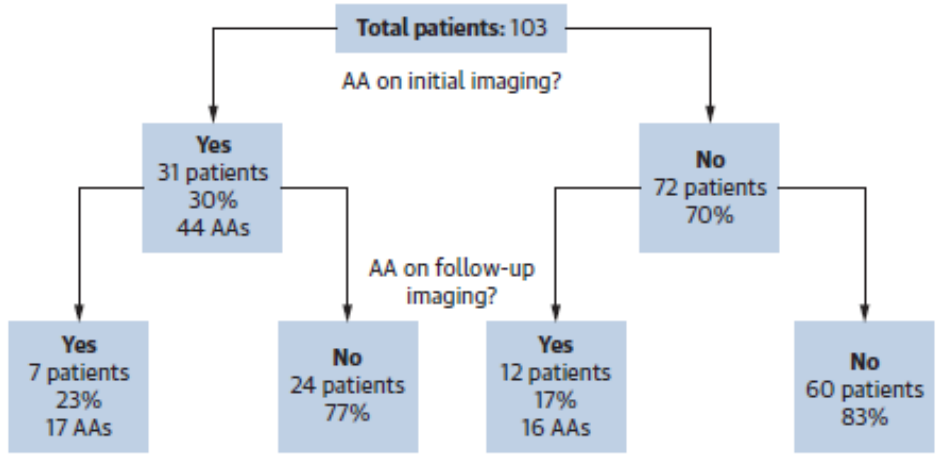
RESULTS A total of 103 patients (53% female) from 60 families with LDS 1 through 5 caused by pathogenic/likely pathogenic variants in *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, and *TGFB3* were included. The median age was 44 years, and median follow-up was 6 years. In total, 77 AAs were identified in 43 patients: 17 AAs in 9 patients with *TGFBR1* variants, 33 AAs in 15 patients with *TGFBR2*, 15 AAs in 8 patients with *SMAD3*, 9 AAs in 8 patients with *TGFB2*, and 3 AAs in 3 patients with *TGFB3*. The median age at AA diagnosis was 40 years; 75% of AAs were in the arch vessels or cerebral circulation. On univariate analysis, aortic event (type A/B dissection or prophylactic aortic surgery) at baseline and prophylactic aortic surgery at baseline were associated with the presence of an AA. Hypertelorism, bifid uvula, and arterial tortuosity approached statistical significance. A multivariate model to predict AA included baseline prophylactic aortic surgery and arterial tortuosity. Of those with vs without AA on initial imaging, 61% and 35%, respectively, presented with previous aortic events. Seventeen percent of AAs enlarged over time, and 38% of AAs that enlarged led to clinical events (prophylactic surgery, dissection, or rupture). Overall, AA-related events occurred in 22% of AAs and throughout the arterial tree. AAs were repaired by open surgical and endovascular techniques.

CONCLUSIONS AAs commonly occur in patients with LDS and may occur throughout the arterial tree. Importantly, AAs may lead to clinical events including arterial dissection and rupture. Head to pelvis imaging at diagnosis and during follow-up is recommended in LDS to evaluate for AAs and their complications. (JACC. 2025;85:2343-2352) © 2025 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by Editor Emeritus Dr Valentin Fuster on www.jacc.org/journal/jacc.

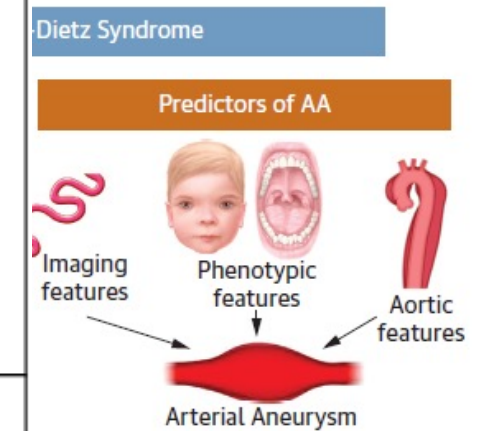
From the [a]Washington University in St Louis School of Medicine, St Louis, Missouri, USA; [b]Department of Neurosurgery, Washington University School in St Louis School of Medicine, St Louis, Missouri, USA; [c]Cardiovascular Division, Department of Medicine, Washington University in St Louis School of Medicine, St Louis, Missouri, USA; and the [d]Department of Internal Medicine, McGovern Medical School, University of Texas Health Science Center, Houston, Texas, USA.

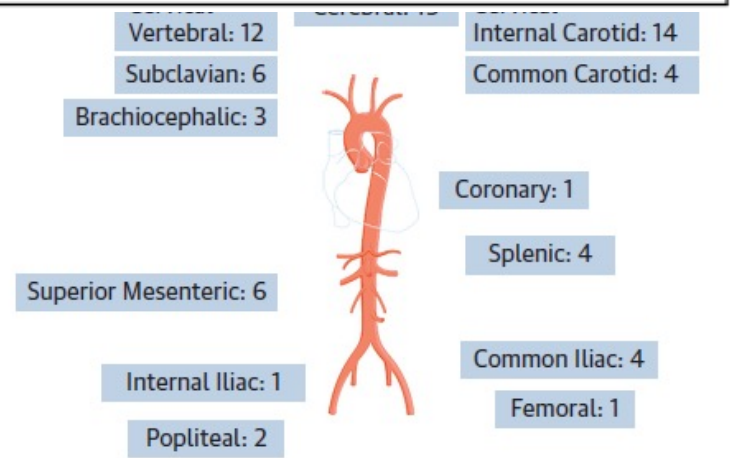
FIGURE 1 Identification of AAs on Initial and Follow-Up Imaging

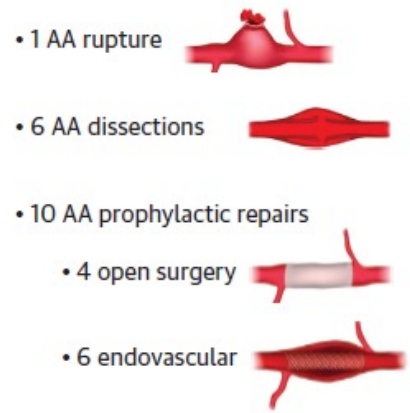


The number and percentage of patients who had or did not have arterial aneurysms (AAs) and total number of AAs observed on initial imaging are shown in the second row. The same data are presented for AAs observed on follow up imaging, stratified by whether or not the patient had an AA observed on initial imaging, in the third row.

ors of Extra-Aortic Arterial Aneurysms in



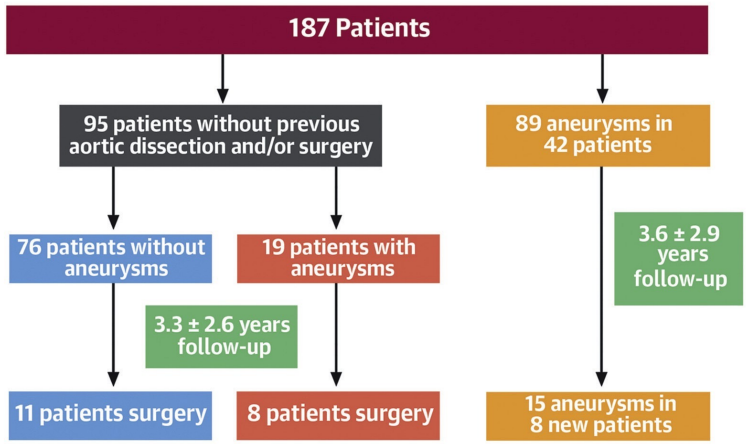


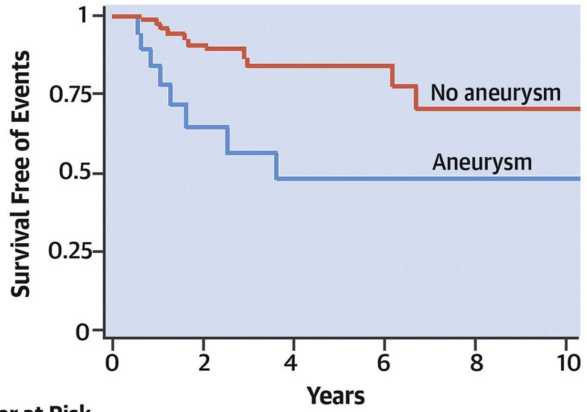


Koefoed AW, et al. JACC. 2025;85(24):2343-2352.

AA = extra-aortic arterial aneurysm; LDS = Loeys-Dietz syndrome.

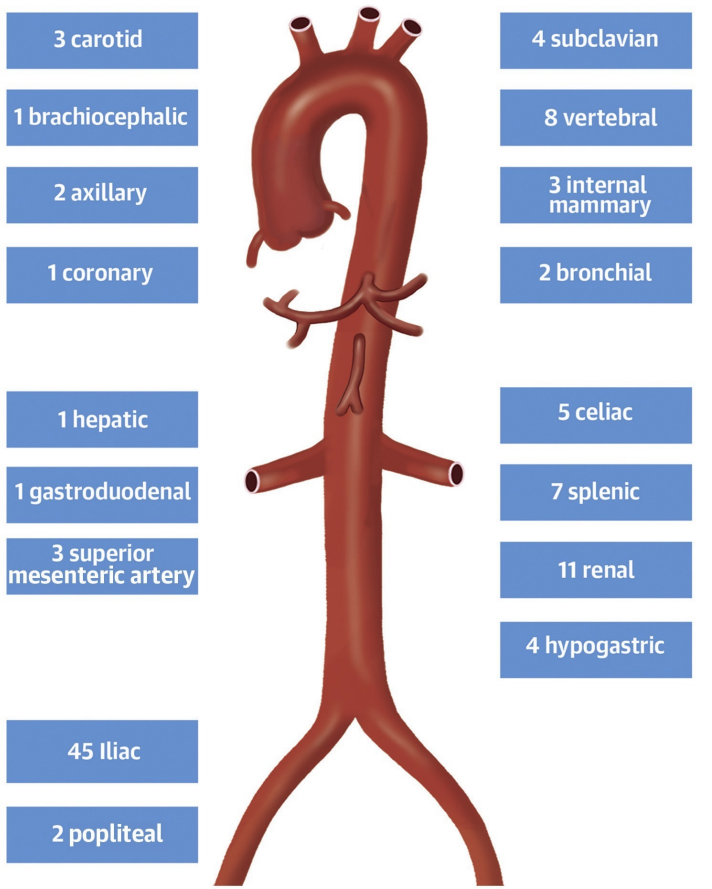
CENTRAL ILLUSTRATION: Aortic Branch Aneurysms in Marfan Syndrome





Number at Risk

No aneurysm	76	81	25	13	6	2
Aneurysm	19	8	4	2	2	1



Lopez-Sainz, A. et al. J Am Coll Cardiol. 2021;77(24):3005-12.

Medical Management and Surveillance in Marfan Syndrome and Loeys-Dietz Syndrome: Conclusions

- In Marfan syndrome and Loeys-Dietz syndrome, pharmacotherapy includes the use of a beta blocker or ARB in maximally tolerated doses, and for those who can tolerate, combination therapy.

- Imaging in Marfan syndrome includes baseline echocardiogram and consideration for cross-sectional imaging with chest MRA or CTA at baseline.

- Annual echocardiogram is recommended in follow-up. After aortic surgery, MRA or CTA is recommended.

- Consideration for abdominal-pelvic aortic imaging in older individuals or with other risk factors for arterial disease.

Medical Management and Surveillance in Marfan Syndrome and Loeys-Dietz Syndrome: Conclusions

- Imaging in Loeys-Dietz syndrome includes echocardiogram and head to pelvis cross-sectional imaging with CTA or MRA at diagnosis.

- Annual echocardiogram is recommended in follow-up with periodic imaging of head to pelvis depending upon age, genetic variant, existing aortic or branch vessel disease (ranging from 1-3 years depending upon aortic segment and other factors)

Alan C. Braverman, MD

abraverm@wustl.edu

Thank you!