

Vascular Ehlers-Danlos Syndrome An Overview Part II: Adult Presentation and management

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THE **MARFAN**
FOUNDATION





Vascular Ehlers-Danlos Syndrome in Adults

Part I: An Overview



- Pathology and features of vEDS in adults
 - Why Accurate Diagnosis of vEDS Matters
 - Management principles in vEDS
 - Screening for arterial pathology in vEDS
-
- Aortic and arterial repair will be discussed in a separate webinar



Diagnostic Criteria for Vascular Ehlers–Danlos Syndromes



Major criteria

1. Family history of vEDS with documented causative variant in *COL3A1*
2. Arterial rupture at a young age
3. Spontaneous sigmoid colon perforation in the absence of known bowel pathology
4. Uterine rupture during the third trimester in the absence of risk factors
5. Carotid-cavernous sinus fistula (CCSF) in the absence of trauma

Minor criteria

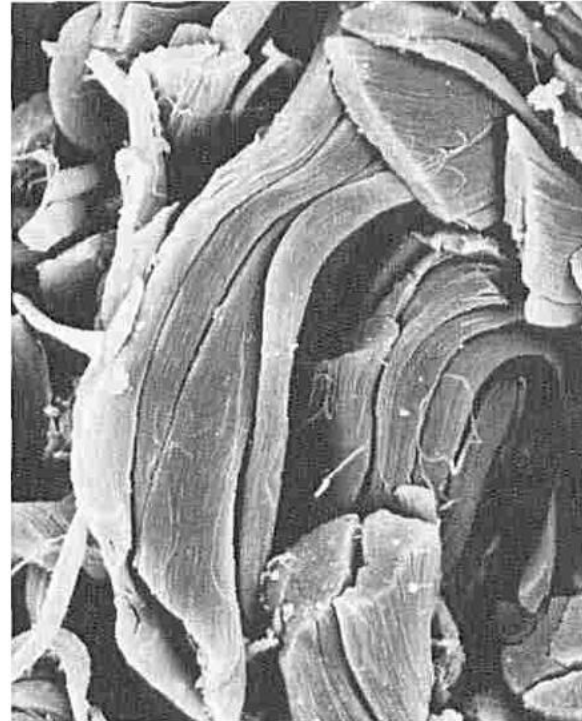
1. Bruising unrelated to identified trauma
2. Thin, translucent skin with increased venous visibility
3. Characteristic facial appearance
4. Spontaneous pneumothorax
5. Acrogeria
6. Talipes equinovarus
7. Congenital hip dislocation
8. Hypermobility of small joints
9. Tendon and muscle rupture
10. Keratoconus
11. Gingival recession and gingival Fragility
12. Early onset varicose veins

Vascular Ehlers-Danlos Syndrome Pathology

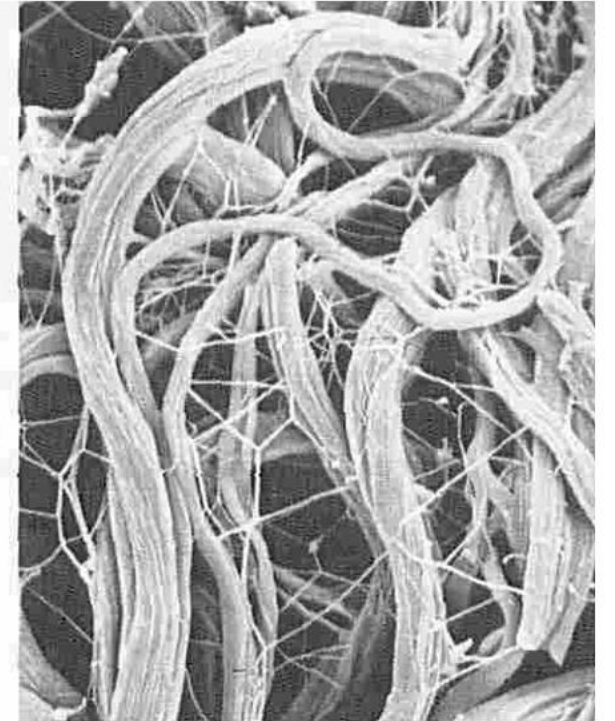
- *COL3A1* encodes procollagen for type III collagen (skin, hollow organs, uterus, arteries)

Pathology:

- Pneumothorax/Hemothorax
- Bowel Perforation
- Aortic/Arterial events
 - Dissection/Aneurysms
 - Ruptures
 - Arteriovenous Fistulae



Control

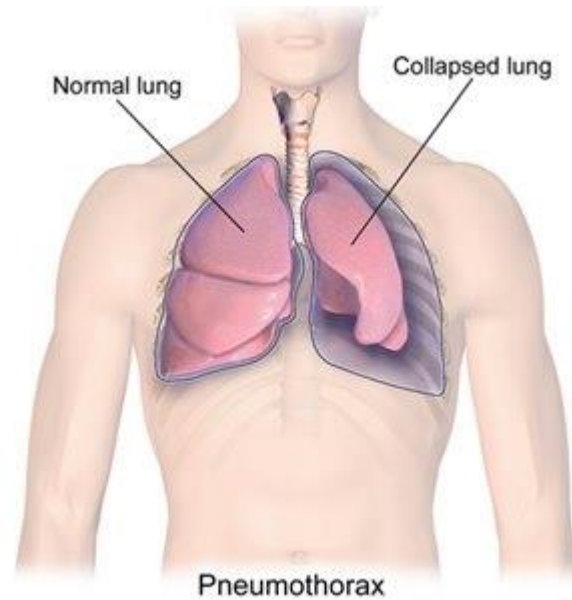


p.Gly373Arg

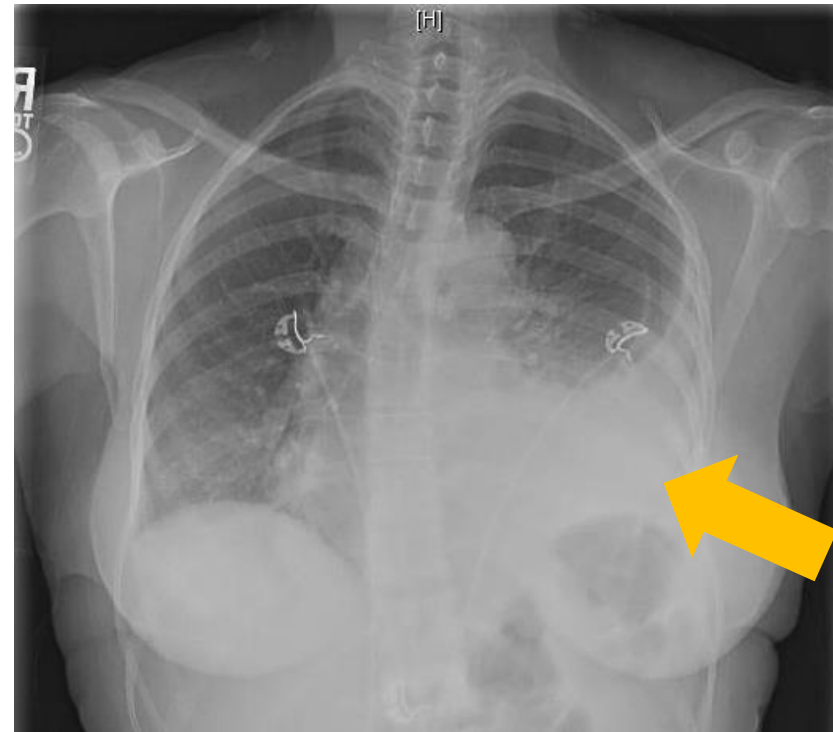
Smith LT. *J Invest Derm*, 1997

Spontaneous Pneumothorax/Hemothorax

occurs when air or blood leaks into the space between the lung and chest wall



Wikiversity Journal of Medicine.
DOI:10.15347/wjm/2014.010. ISSN
20018762.)



Hemothorax




Pneumothorax occurs at a significantly younger age compared to arterial ruptures in individuals with vEDS



RESEARCH ARTICLE

Spontaneous pneumothorax and hemothorax frequently precede the arterial and intestinal complications of vascular Ehlers–Danlos syndrome

Sherene Shalhub , Enid Neptune, Desiree E. Sanchez, Anahita Dua, Nelson Arellano, Nazli B. McDonnell, Dianna M. Milewicz

First published: 22 February 2019 | <https://doi.org/10.1002/ajmg.a.61094>



Spontaneous Gastrointestinal Perforation

- Abdominal pain
- Tender abdomen
- Pain with walking (Peritoneal signs)

Tech Coloproctol. 2018 May;22(5):333-341. doi: 10.1007/s10151-018-1783-4. Epub 2018 Apr 26.

Bowel perforation in type IV vascular Ehlers-Danlos syndrome. A systematic review.

El Masri H¹, Loong TH¹, Meurette G¹, Podevin J¹, Zinzindohoue F², Lehur PA³.

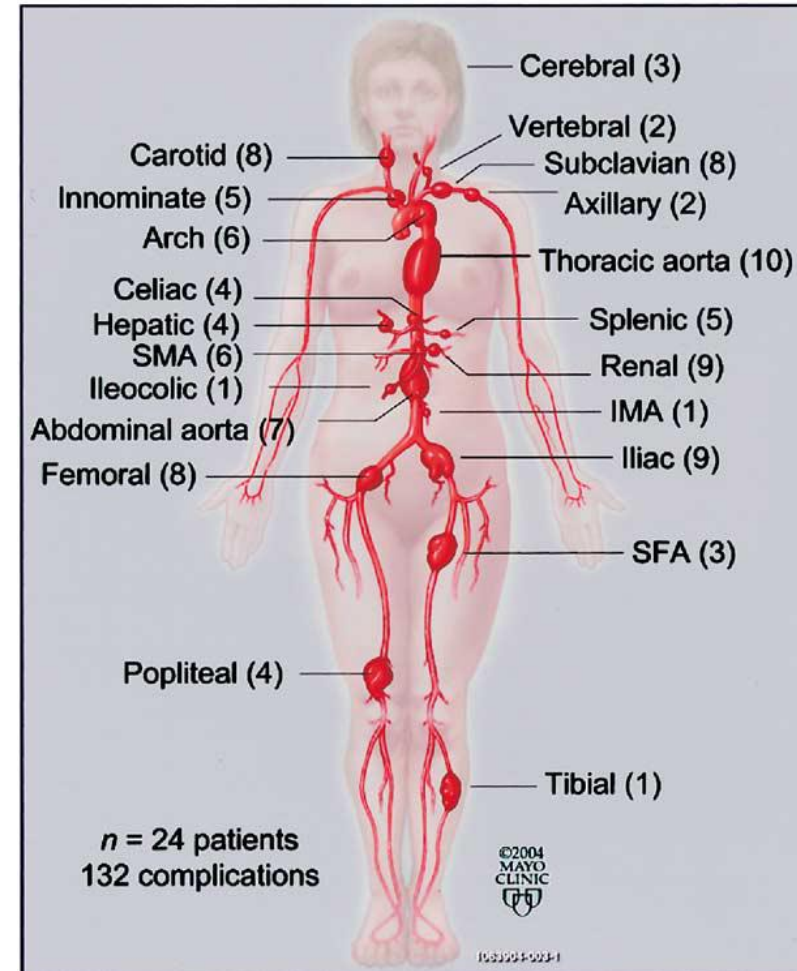
- The most frequent site of perforation:
 - **Colon (sigmoid)**
 - Small bowel
 - Upper rectum
 - stomach
- Re-perforation rate considerably higher in the “partial colectomy with anastomosis” group than in the Hartmann group



Arterial and Aortic Pathology in vEDS

The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: A 30-year experience

Gustavo S. Oderich, MD,^a Jean M. Panneton, MD,^b Thomas C. Bower, MD,^a Noralane M. Lindor, MD,^c
Kenneth J. Cherry, Jr, MD,^a Audra A. Noel, MD,^a Manju Kalra, MBBS,^a Timothy Sullivan, MD,^a and Peter
Gloviczki, MD,^a Rochester, Minn; and Norfolk, Va

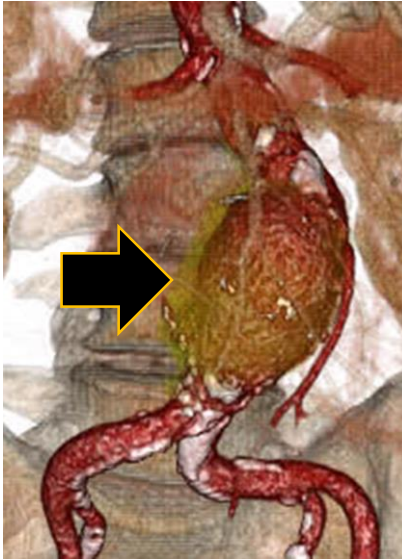


Arterial and Aortic Pathology in vEDS: Aneurysms

Dilatation of the artery to more than 1.5 times the size of the normal.

Usually asymptomatic

Fusiform



Saccular

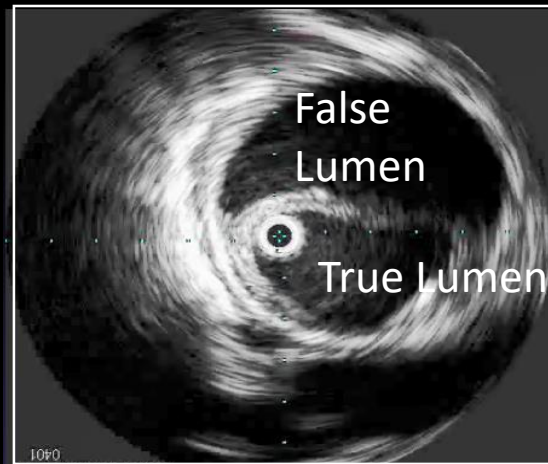
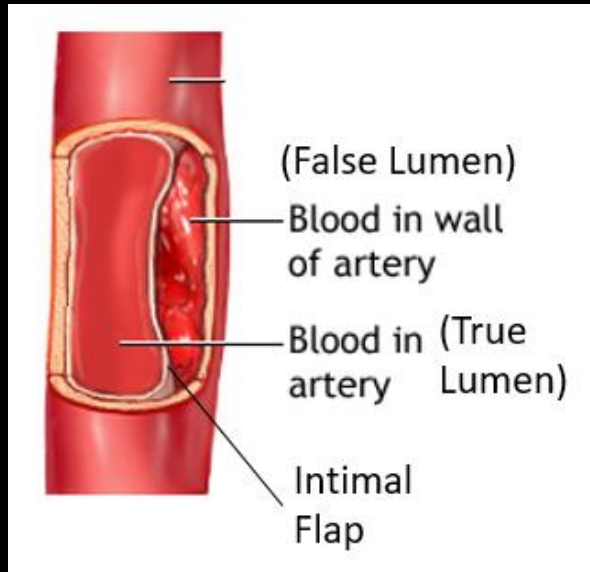


Ruptured Aneurysm

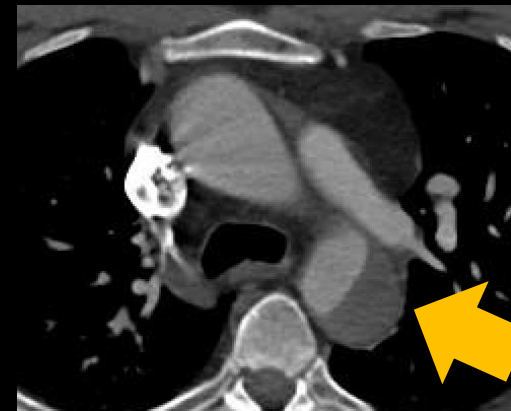
Cause internal bleeding. Presents with Sudden onset severe pain



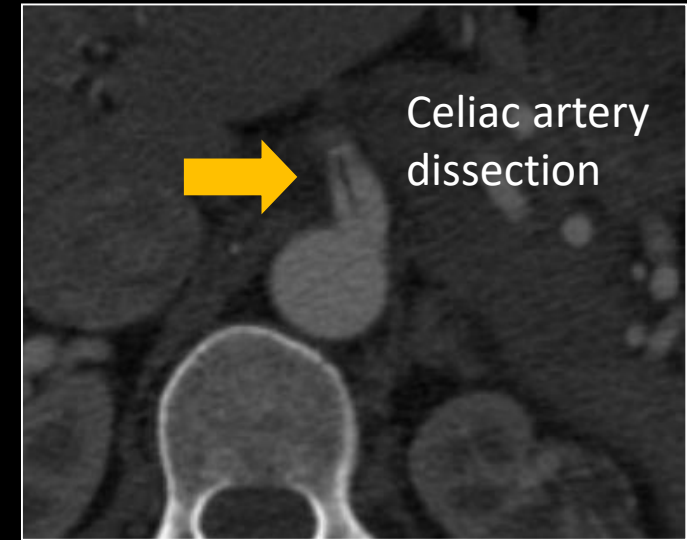
Arterial and Aortic Pathology in vEDS: Dissection



Aortic dissection



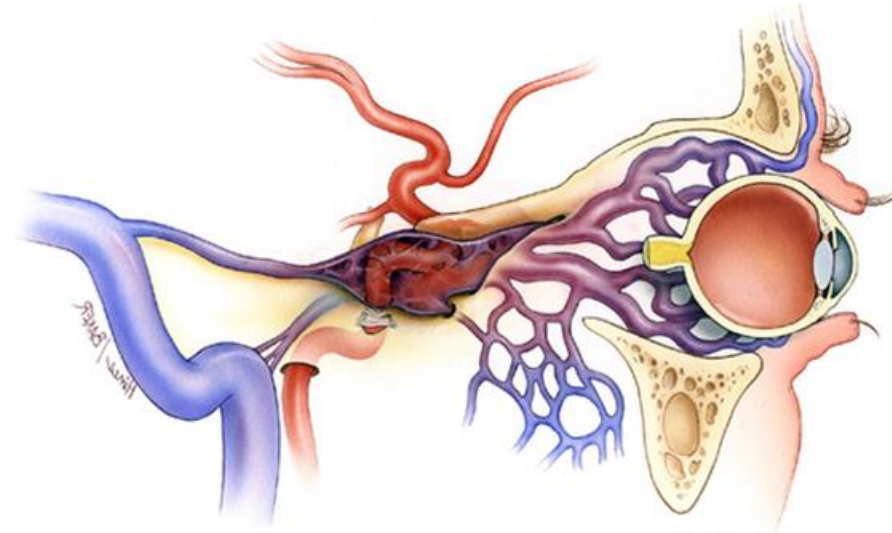
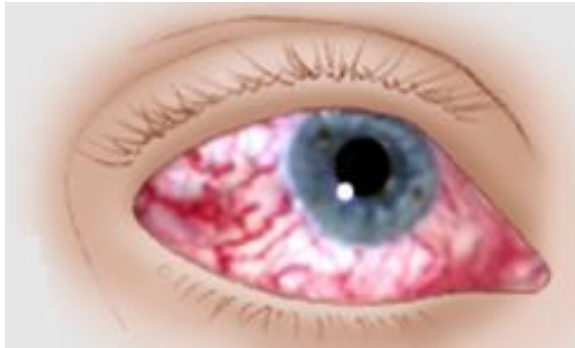
Type B Aortic dissection



External iliac artery dissection

Carotid Cavernous Fistula

- Abnormal communication between the carotid artery and cavernous sinus
 - Bulging eye, which may pulsate
 - Red eye
 - Abnormal eye movement
 - Pain



Adham et al, Orphanet Journal of Rare Diseases, 2018



Facial Features



- N=68
- 61% had facial features
- Prominent eyes
- Thin lips and philtrum
- Thin, pinched nose
- Hollow cheeks
- Attached ear lobes



Physical Exam Findings



Skin: Visible veins
soft velvety skin



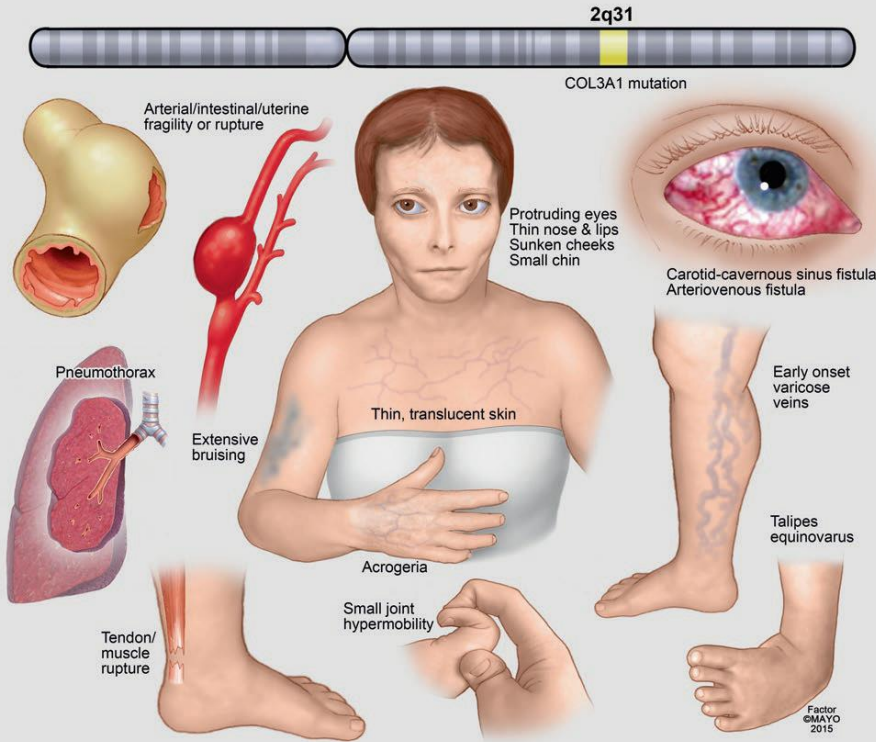


Why Accurate Diagnosis of vEDS Matters

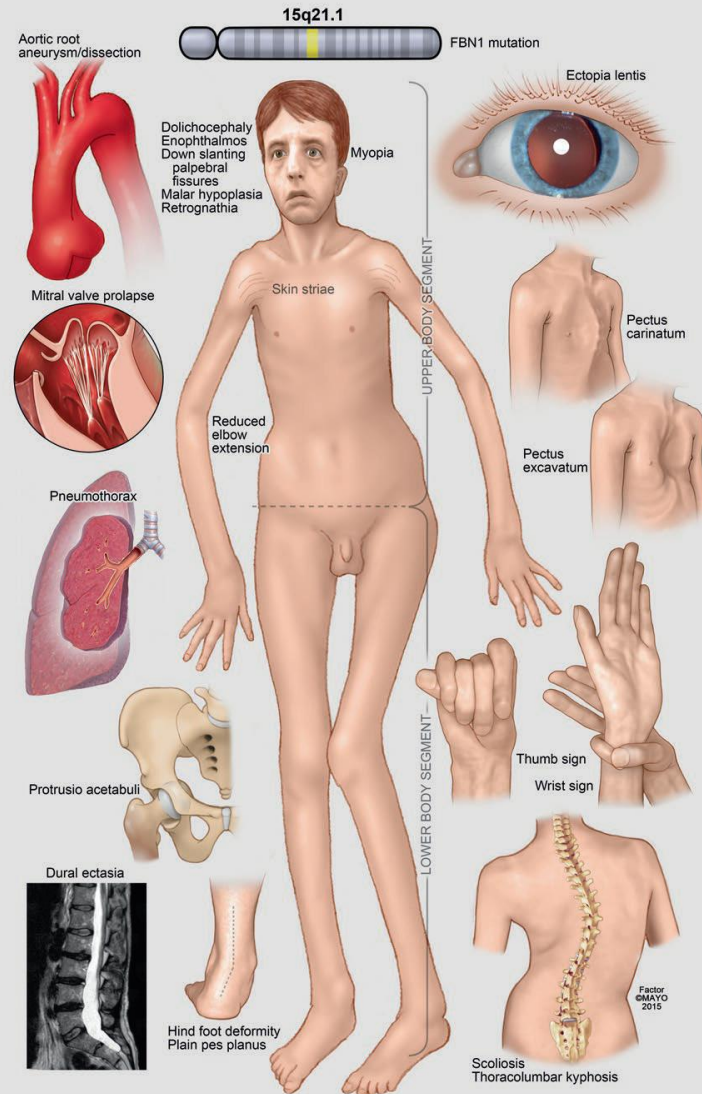


1. Overlapping features with other syndromes

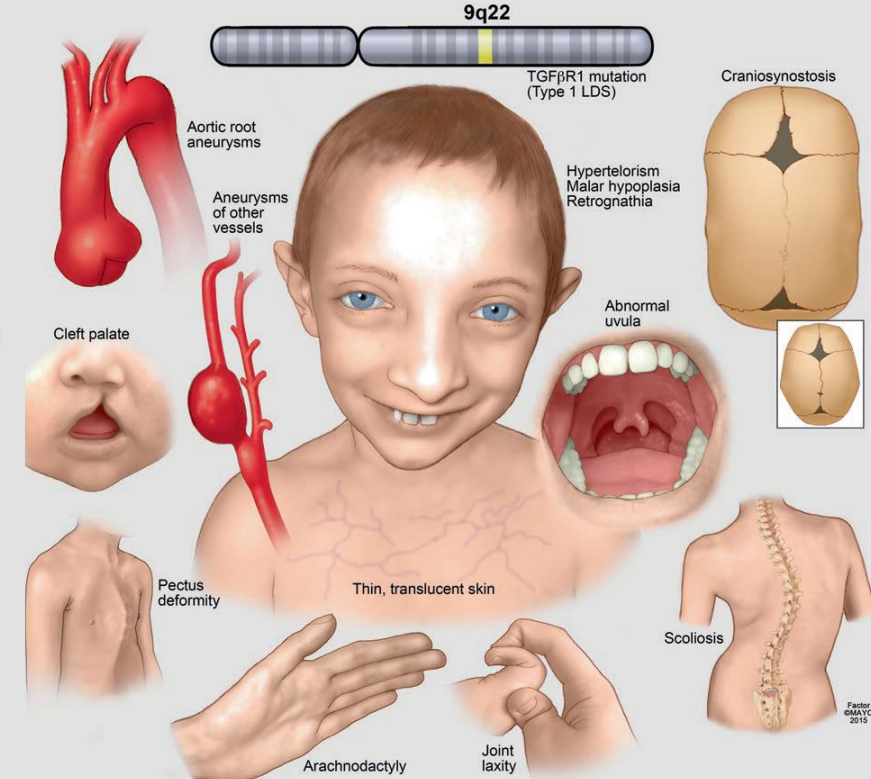
Vascular Ehlers-Danlos Syndrome



Marfan Syndrome



Loeys Dietz Syndrome





Why Accurate Diagnosis of vEDS Matters



1. Overlapping features with other syndromes
2. Genotype-Phenotype correlation



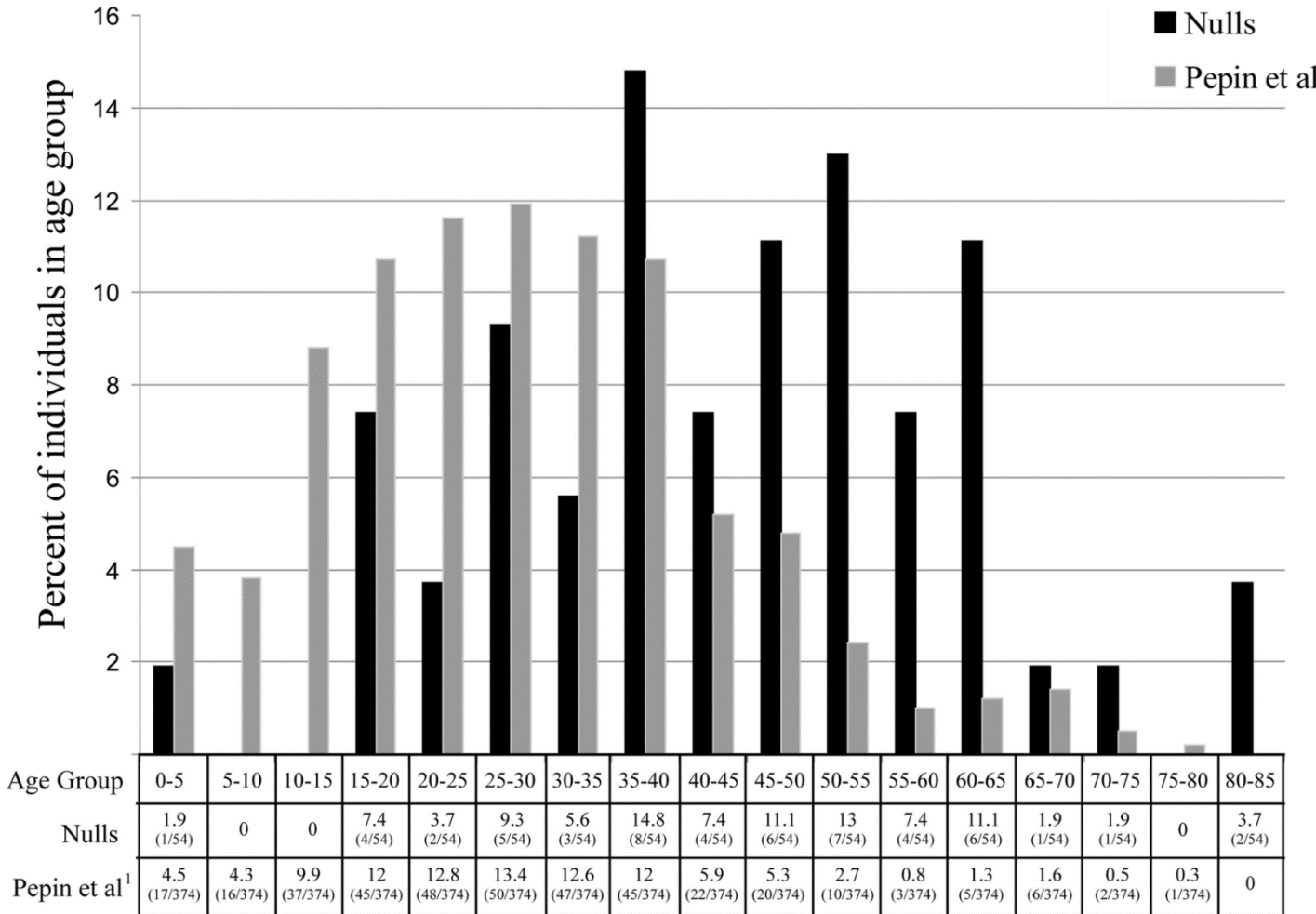
COL3A1 haploinsufficiency results in a variety of Ehlers-Danlos syndrome type IV with delayed onset of complications and longer life expectancy



Dru F. Leistriz, MS¹, Melanie G. Pepin, MS¹, Ulrike Schwarze, MD¹, and Peter H. Byers, MD^{1,2}

Single functional copy of a gene

50% of normal type III collagen





Why Accurate Diagnosis of vEDS Matters

1. Overlapping features with other syndromes
2. Genotype-Phenotype correlation
3. Knowing the diagnosis improves outcomes
 - Aggressive risk factor modification:
 - Smoking cessation
 - Exercise recommendations
 - Assessment and treatment for hypertension
 - Tailor operative techniques



A multi-institutional experience in the aortic and arterial pathology in individuals with genetically confirmed Vascular Ehlers Danlos Syndrome



Molecular diagnosis in vascular Ehlers-Danlos syndrome predicts pattern of arterial involvement and outcomes

Sherene Shalhub, MD, MPH,^a James H. Black III, MD,^b Alana C. Cecchi, MS,^c Zhi Xu, PhD,^d Ben F. Griswold, BS,^d Hazim J. Safi, MD,^c Dianna M. Milewicz, MD, PhD,^c and Nazli B. McDonnell, MD, PhD,^d *Seattle, Wash; Baltimore, Md; and Houston, Tex*

N=68 *Journal of Vascular Surgery, July 2014*

Arterial pathology in vEDS individuals is related to the underlying *COL3A1* mutation type (Haploinsufficiency vs. other subtypes)

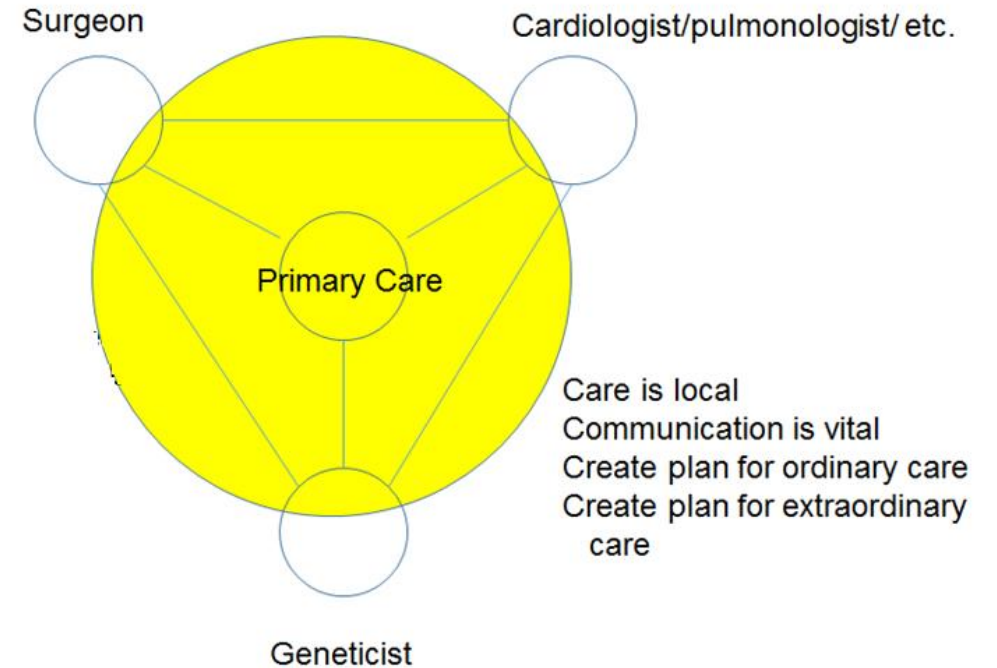
Haploinsufficiency: milder phenotype, more aortic pathology

Patients with an established preoperative diagnosis treated in an elective setting have significantly improved outcomes compared with patients who undergo emergency repair and when the diagnosis is not known



Why Accurate Diagnosis of vEDS Matters

1. Overlapping features with other syndromes
2. Knowing the diagnosis improves outcomes
3. Knowing the diagnosis improves outcomes
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 - Tailor operative techniques
4. Multidisciplinary care (Care Team)





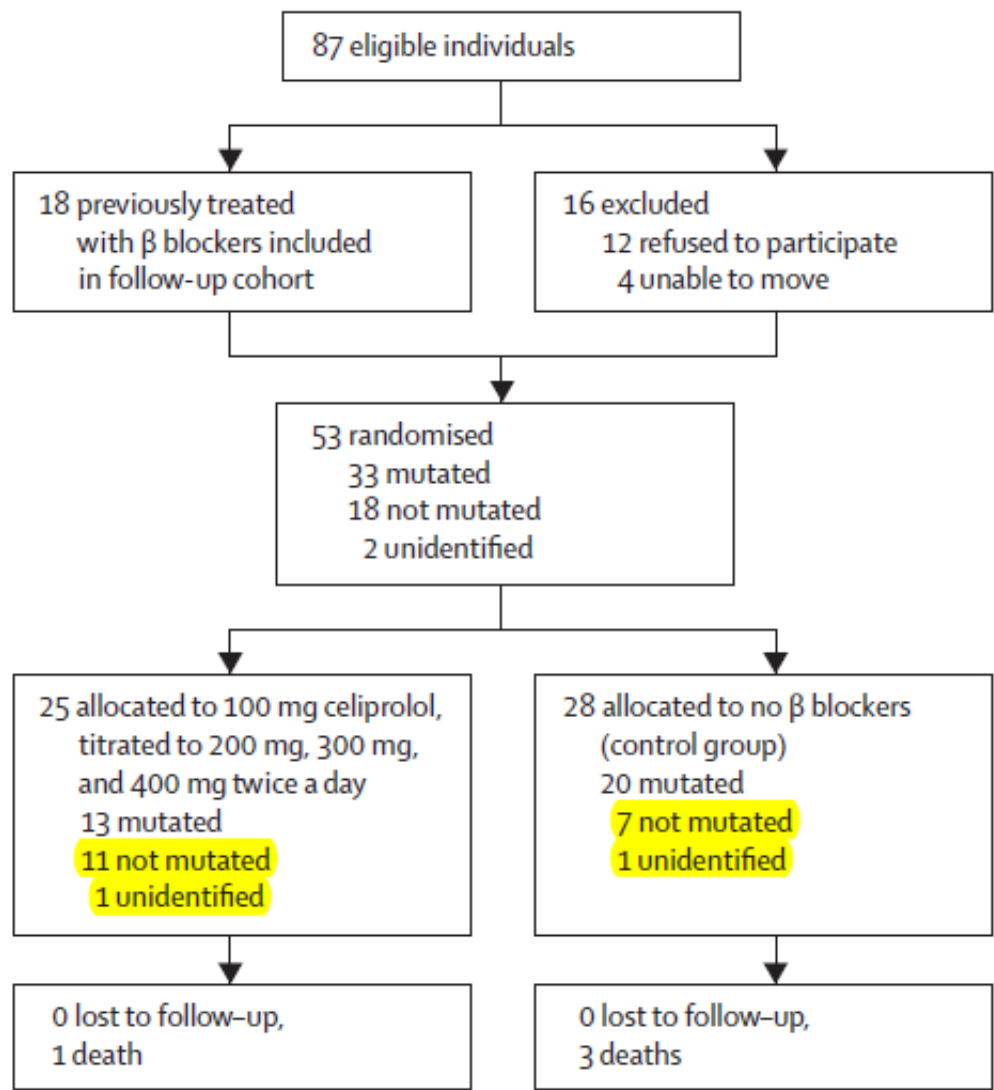
Why Accurate Diagnosis of vEDS Matters

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3. Knowing the diagnosis improves outcomes:
 - Aggressive risk factor modification:
 - Smoking cessation
 - Exercise recommendations
 - Assessment and treatment for hypertension
 - Tailor operative techniques
4. Multidisciplinary care (Care Team)
5. Research implications

Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial

Lancet, 2010

Kim-Thanh Ong, Jérôme Perdu, Julie De Backer, Erwan Bozec, Patrick Collignon, Joseph Emmerich, Anne-Laure Fauret, Jean-Noël Fiessinger, Dominique P Germain, Gabriella Georgesco, Jean-Sebastien Hulot, Anne De Paepe, Henri Plauchu, Xavier Jeunemaitre, Stéphane Laurent, Pierre Boutouyrie



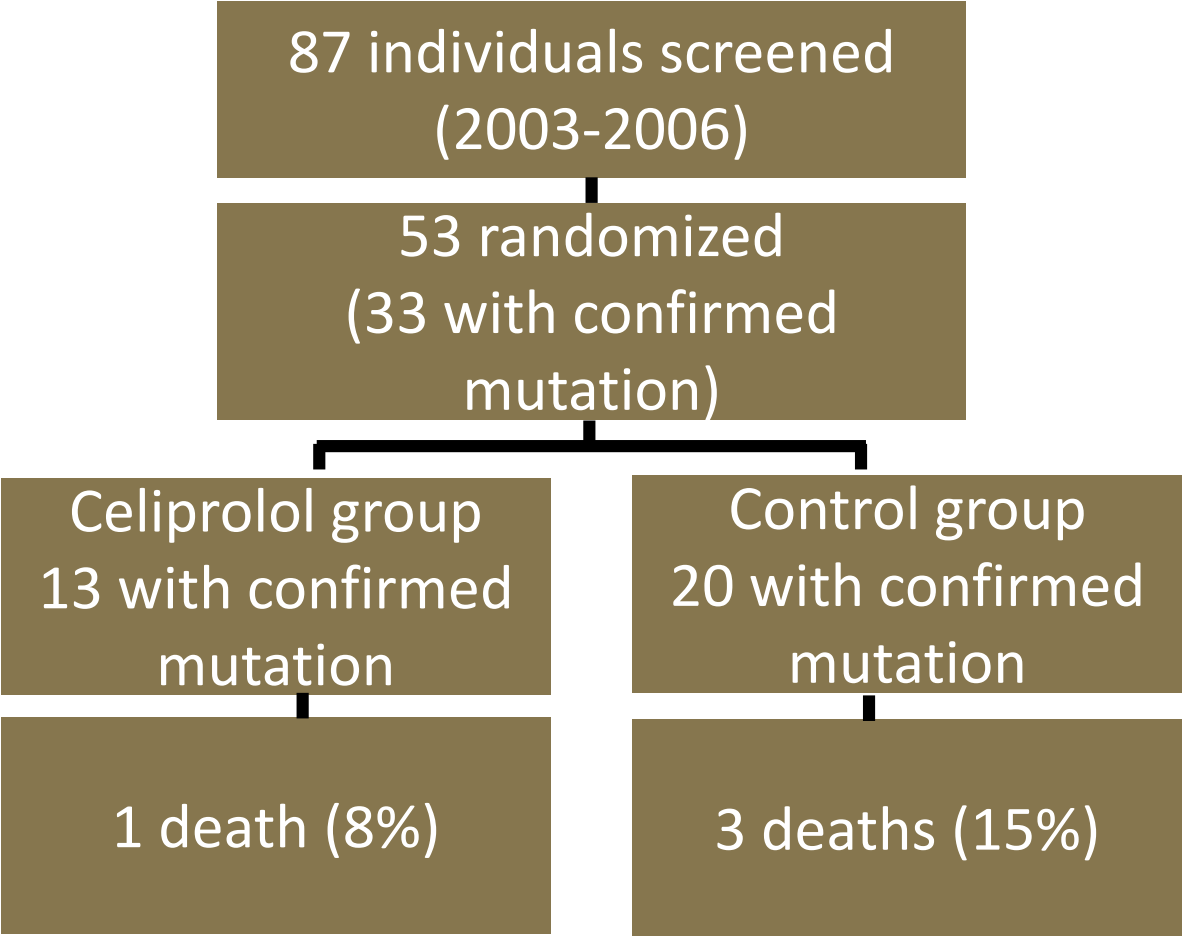
Celiprolol BID to a maximum of 400 mg per day

Male, 31	Control	Death or iliac artery rupture within 4 months of enrollment. Underwent open abdominal aortic repair then died from type A dissection
Male, 28	Control	Hypogastric artery rupture
Female, 51	Control	Spontaneous cerebral hematoma
Female, 38	Control	Spontaneous hematoma of psoas muscle with blood suffusion
Male, 25	Control	Carotid dissection
Male, 28	Control	Death or aortic dissection
Female, 24	Control	Carotid dissection
Female, 34	Control	Carotid-cavernous sinus fistula
Female, 31	Control	Carotid-cavernous sinus fistula
Female, 42	Control	Primitive iliac artery dissection
Male, 45	Control	Sudden death after acute lumbar pain
Male, 19	Celiprolol	Sudden death after acute chest pain radiating to the right arm
Male, 19	Celiprolol	Hemoptysis (recurrent)

Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial

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vEDS Management Principles

Aggressive risk factor modification

- Smoking cessation
- Assessment and treatment for hypertension
- Daily walking
- Screening program



Medical Management

- Beta blockers (Celiprolol data)
- Vitamin C (Anecdotal)
- Aspirin (aneurysms/dissections)
- Doxycycline (Aneurysm data)
- Anti-inflammatory diet

Aortic and arterial repair will be discussed in a separate webinar



Exercise Recommendations



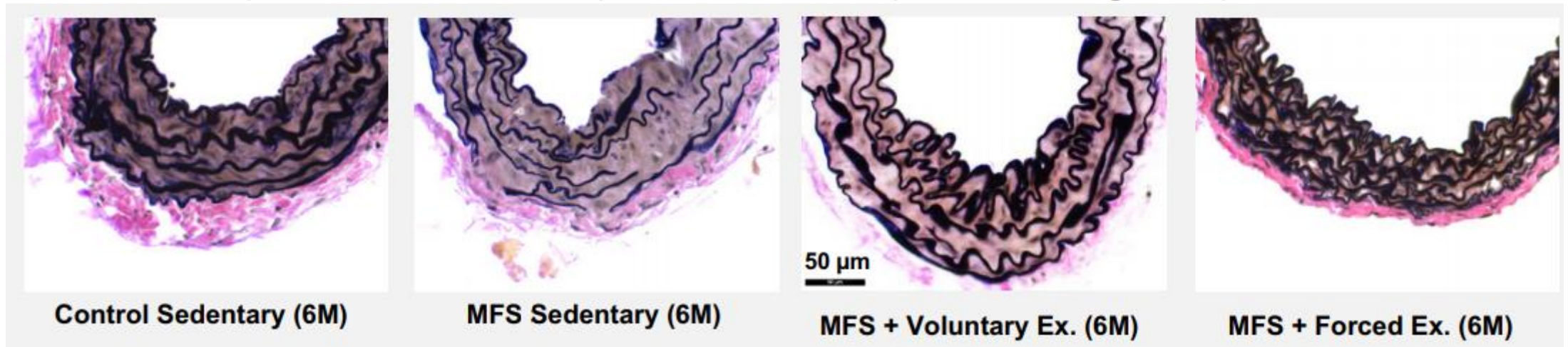
RESEARCH ARTICLE

J Appl Physiol 123: 147–160, 2017.

First published April 6, 2017; doi:10.1152/jappphysiol.00132.2017.

Mild aerobic exercise blocks elastin fiber fragmentation and aortic dilatation in a mouse model of Marfan syndrome associated aortic aneurysm

Christine Gibson,¹ Cory Nielsen,¹ Ramona Alex,¹ Kimbal Cooper,¹ Michael Farney,¹ Douglas Gaufin,¹ Jason Z. Cui,³ Cornelis van Breemen,³ Tom L. Broderick,² Johana Vallejo-Elias,² and Mitra Esfandiarei^{1,3}



Mild aerobic exercise at 55% intensity (55% VO₂max)



Fluoroquinolones



Drugs

Avelox (moxifloxacin)
Baxdela (delafloxacin)
Cipro (ciprofloxacin)
Factive (gemifloxacin)
Levaquin (levofloxacin)
Generic ofloxacin

availability

FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects



SHARE



TWEET



LINKEDIN



PIN IT



EMAIL



PRINT

[Drug Safety Communications](#)

[Drug Shortages](#)



[Postmarket Drug Safety
Information for Patients and
Providers](#)



This information is an update to the FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together issued on **May 12, 2016**



Screening for arterial pathology in vEDS

- Vascular Surveillance
- Goal: discover asymptomatic aneurysms/dissections
- Can also be used for diagnostic purposes

Duplex Ultrasound

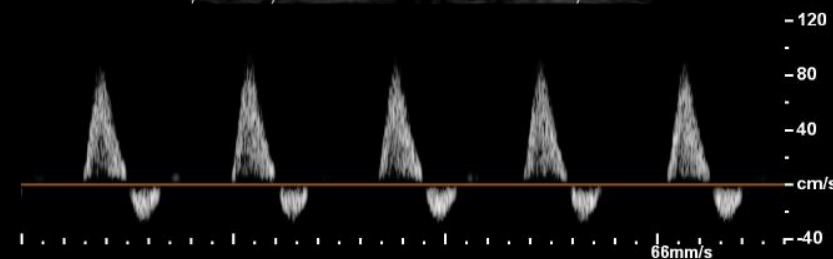
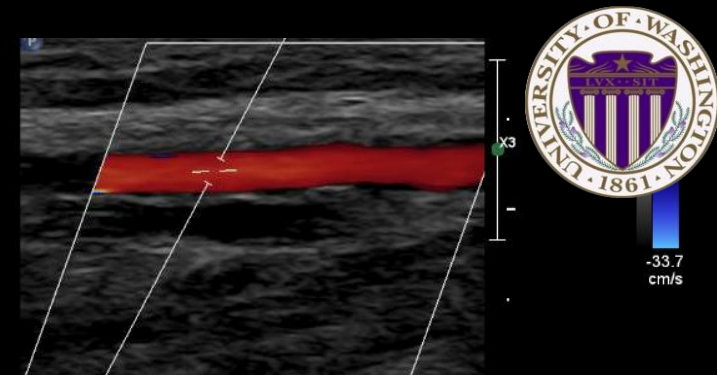
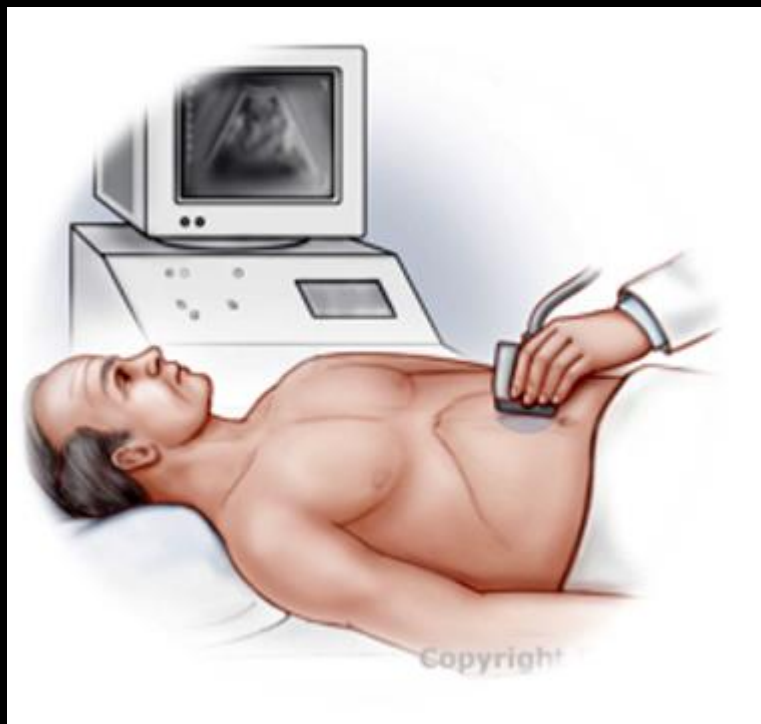
Computed Tomography (CT)

Magnetic Resonance
Imaging



Duplex Ultrasonography

- No radiation
- Works anywhere except the chest





Computerized Axial Tomography (CT)

- CT scan, CAT scan
- What does it entail?
 - Radiation exposure
 - Starting an IV
 - Contrast (also called dye)
 - Computer – imaging reconstruction
- Oral vs. IV contrast
- CT angiogram (CTA)





Magnetic Resonance (MR) Imaging

What does it entail?

- uses strong magnetic fields & radio waves
- Starting an IV
- May need sedation
- Contrast (also called dye)
- Computer – imaging reconstruction
- Limitations





Summary of vEDS Management Principles

- Accurate diagnosis of vEDS is an imperative (genetic testing)
- Management principles: Holistic care
 - Creating a care team
 - Risk factor modification
 - Medical management
 - Screening
- The future in translational vEDS research:
 - A comprehensive knowledge of the natural history
 - Accurate and detailed phenotypes description and knowledge of the genotype
 - Patient input into research priorities



Vascular Ehlers-Danlos Syndrome Collaborative (2018)

Patient
Centered
Outcomes
Research
Institute



Infrastructure

Relationships

Capacity
Building



Virtual Research Network (VRN)

- Group of 300+ stakeholders, assembled via remote outreach through existing relationships and networks of Collaborative members
- Responsible for responding to surveys from Collaborative and assisting with data collection and outreach

Stakeholder Group

- Group of 25 people (patients, families, clinicians, and researchers) who meet monthly via teleconference
- Responsible for giving feedback on survey materials, outreach plans, and contributing meaningfully to major decisions

Advisory Group

- Five core leaders (includes a patient partner, a family member, a researcher, and a clinician), meets monthly via teleconference and leads stakeholder group meetings
- Responsible for strategic planning, event planning, and preparing funding applications on behalf of Collaborative



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