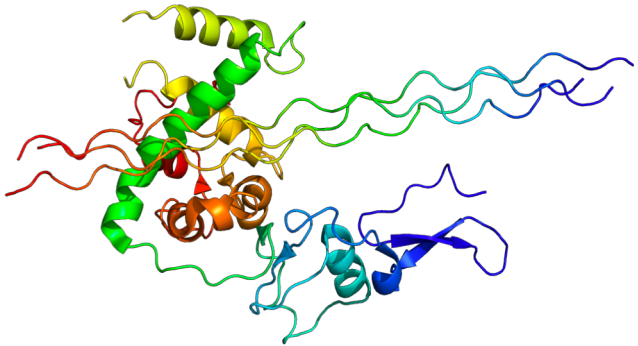
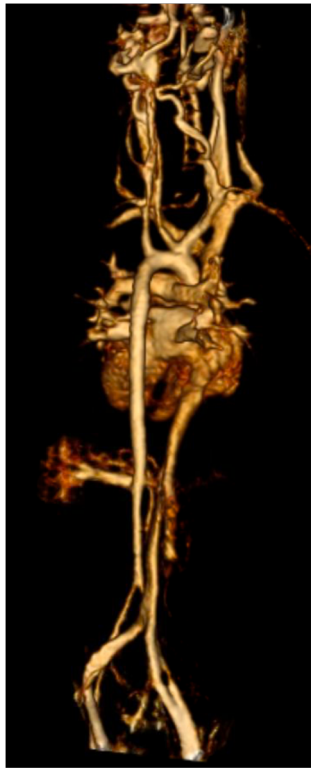
Vascular Ehlers-Danlos syndrome - An Overview Part I: Etiology, pediatric presentation and management





Shaine A. Morris, MD, MPH
Associate Professor, Pediatrics – Cardiology
Medical Director, Cardiovascular Genetics

Baylor College of Medicine

Texas Children's Hospital

vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

THE MARFAN FOUNDATION

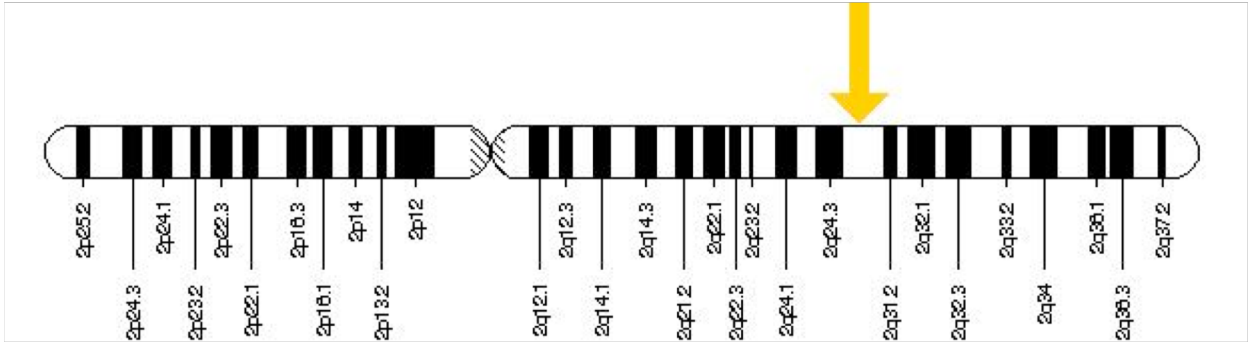
Objectives

- Genetics of vEDS
- Learn about what affects children with vEDS
- Management in children with vEDS

What is Vascular EDS?

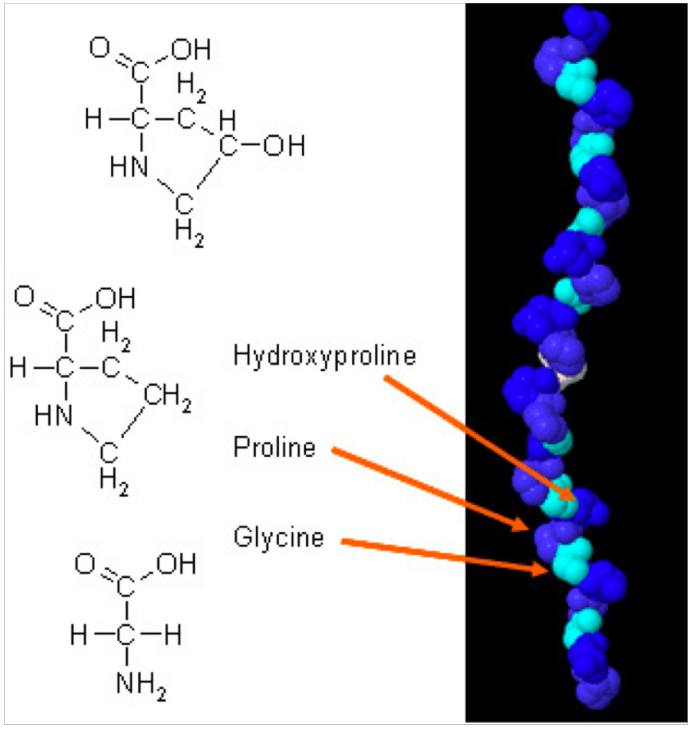
Vascular EDS

- Estimated to be present in 1 in 50,000-200,000 people
- A rare type of EDS (EDS IV) caused by a mutation in the *COL3A1* gene, which encodes part of type III collagen



Vascular EDS

- Collagen is a tough, fiber-like protein that makes up about a third of body protein.
- Type III collagen is found in extensible connective tissues such as skin, lung, uterus, intestine and the vascular system



Type 3 Collagen

https://proteopedia.org/wiki/index.php/Image:Collagen_%28alpha_chain%29.jpg

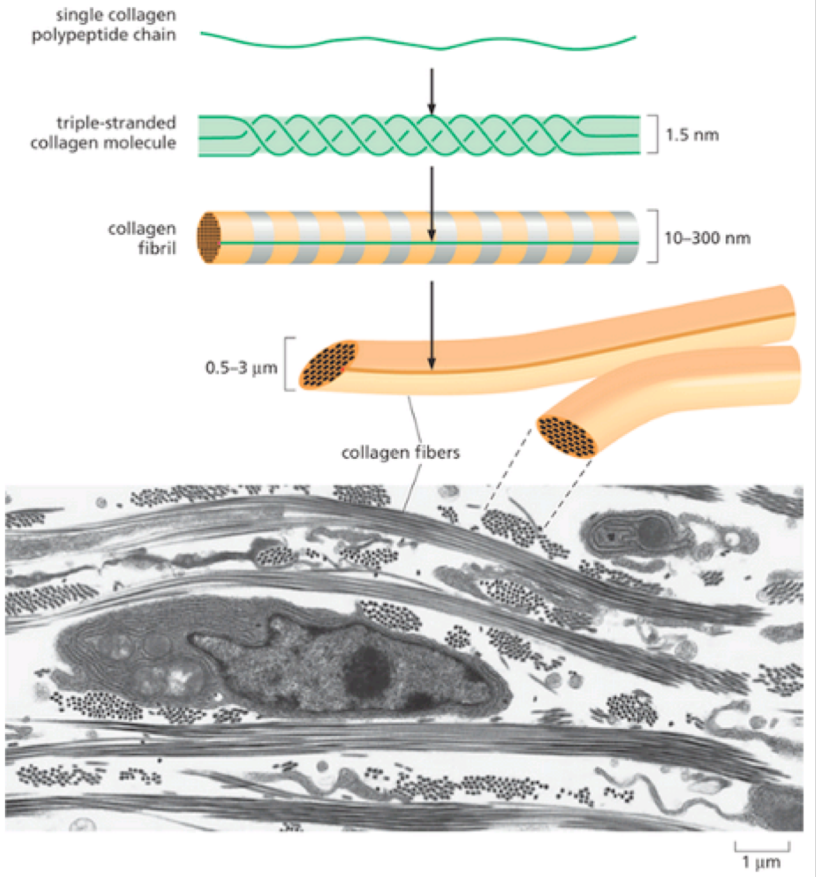


Figure 20–9 **Collagen fibrils are organized into bundles.** The... More »

Source: Essential Cell Biology, 3rd Ed., by Bruce Alberts; Chapter 20

Genetics of Vascular EDS

- Autosomal dominant inherited disorder caused by type III procollagen gene (COL3A1) mutations
  - Only need 1 affected gene to have disease
  - May get from 1 parent or may be spontaneous aka “de novo”
  - 50% of the COL3A1 mutations are inherited from an affected parent, and 50% are de novo
  - Each child of an affected individual has a 50% chance of inheriting the mutation and developing the disorder

Baylor College of Medicine

Texas Children's Hospital

vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

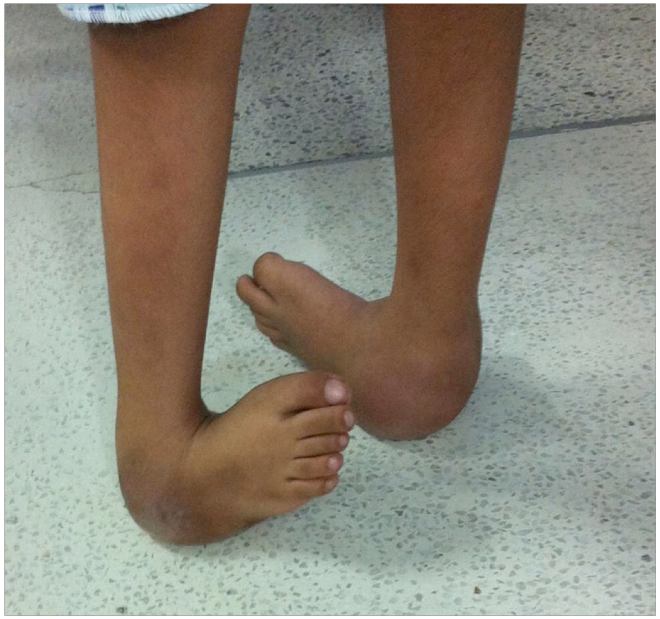
THE MARFAN FOUNDATION

Vascular EDS in children

- In children, the features most commonly identified as the reason for testing are:
  - Family history (~60%)
  - Skin/skeletal signs: easy bruising/hematomas, thin skin, and joint hypermobility
  - Presentation with a critical event is rare
- It is common for child abuse to be suspected given the significant bruising in some cases

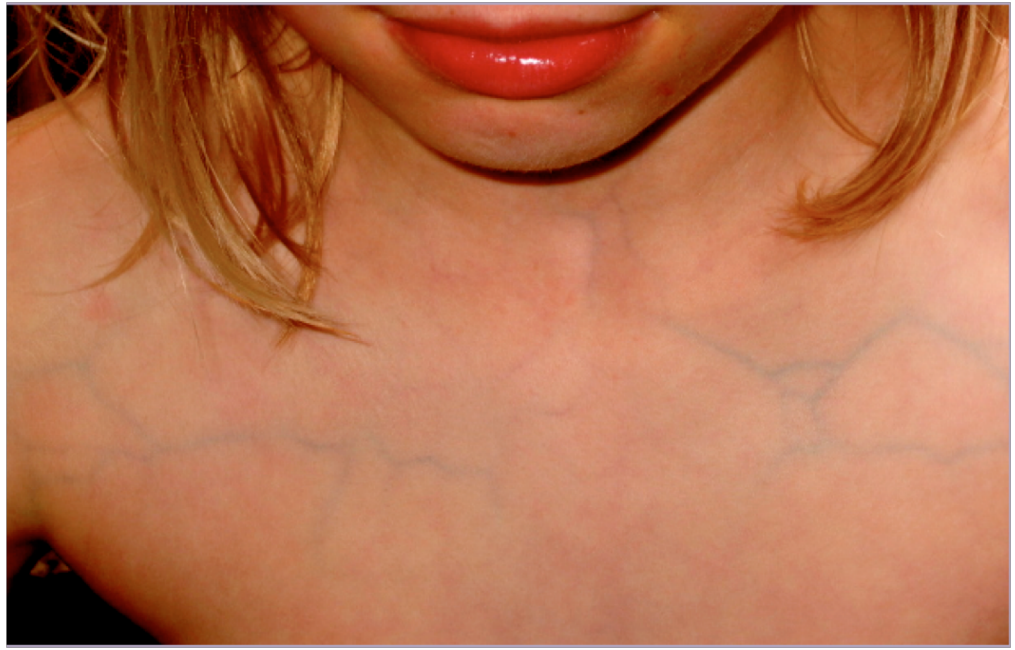
Vascular EDS in children

- Infants with the condition may be born with
  - Clubfoot, which causes the foot to turn inward and downward (8%)
  - Hip dislocations (1%)
  - Limb deficiency/amniotic band syndrome (1%)



Vascular EDS Characteristics

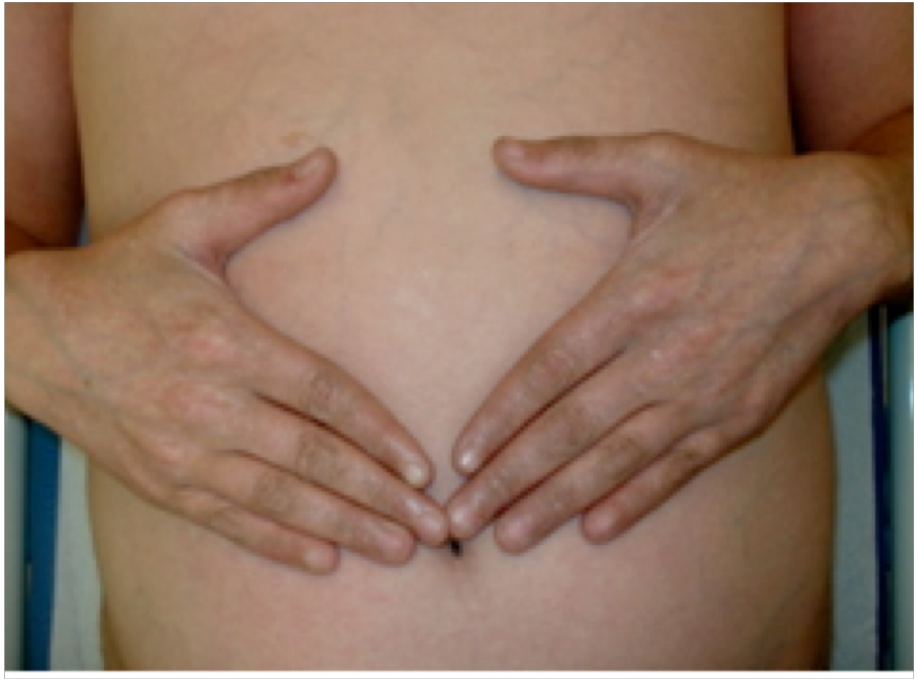
Thin, translucent skin: veins are visible beneath the skin, especially on chest / abdomen



1. Morais et al. *Dermatology Online Journal* 2011
2. EDSToday.org 2013

Vascular EDS Characteristics

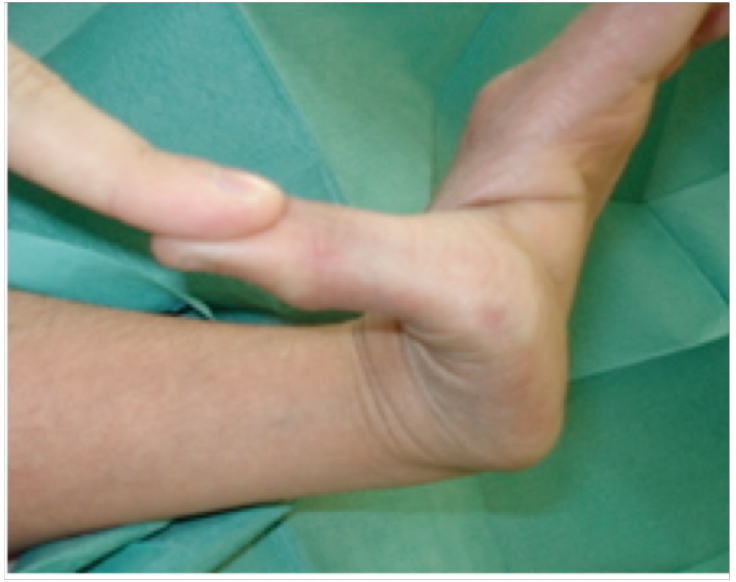
- Unlike people with other forms of EDS, people with Vascular EDS have skin that is soft but not overly stretchy
- Hands and feet may appear aged
- Easy bruising



Morais et al. *Dermatology Online Journal* 2011

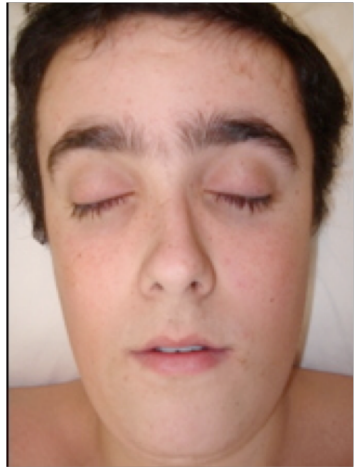
Vascular EDS Characteristics

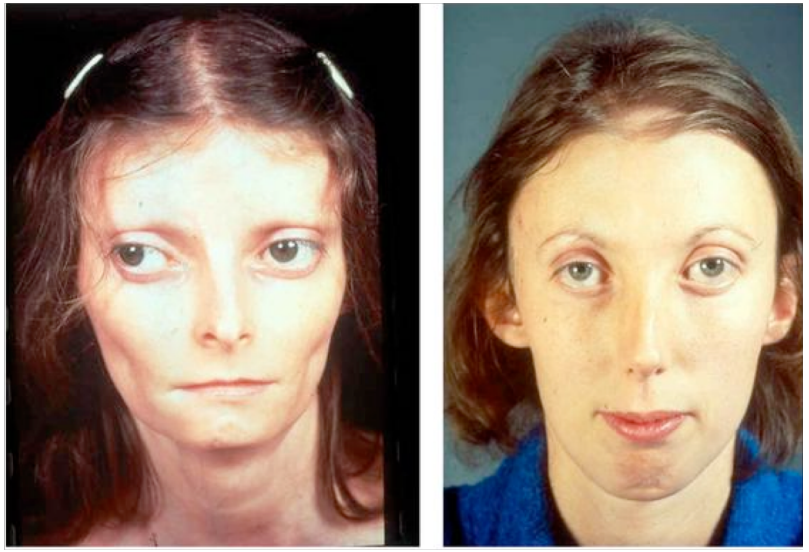
- Joint hypermobility (able to bend further than expected at joints)
- Easy tearing of tendons and muscles
- Painfully swollen veins in the legs
- Slow wound healing following injury or surgery



Vascular EDS Characteristics

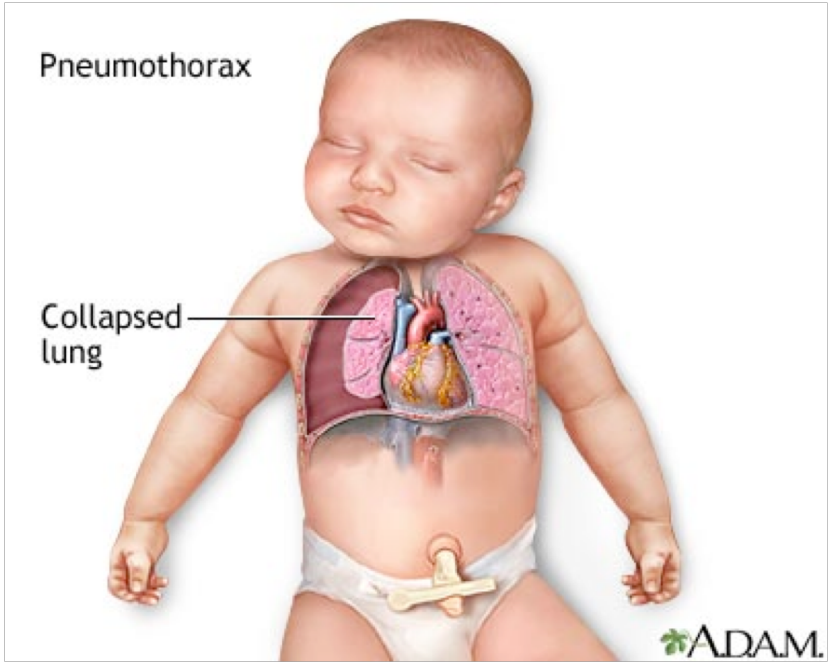
- Characteristic facial features
  - Protruding eyes
  - Thin “pinched” nose and lips
  - Sunken cheeks
  - Small chin

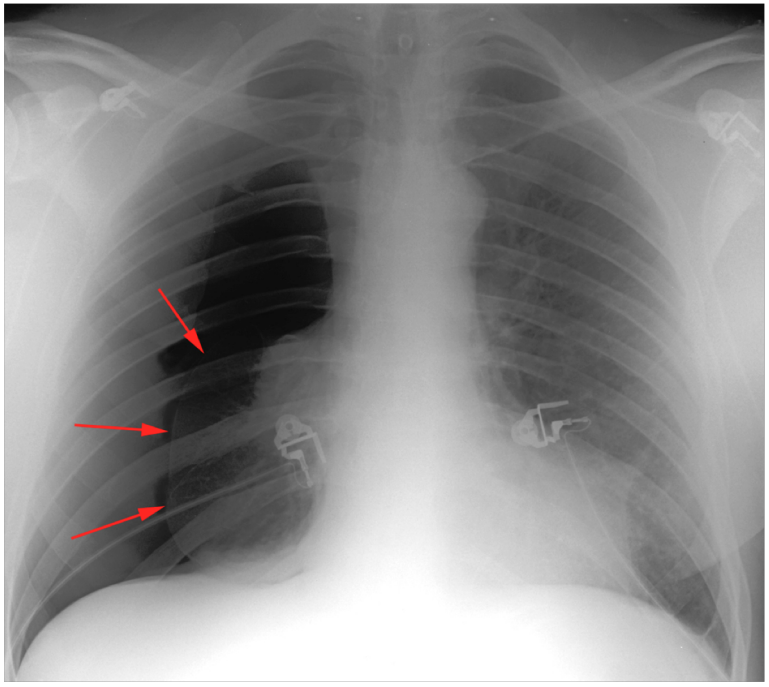




1. Morais et al. *Dermatology Online Journal* 2011
2. Vanakker, Hemelsoet, De Paepe. Stroke Research and Treatment 2011

Complications - Pneumothorax

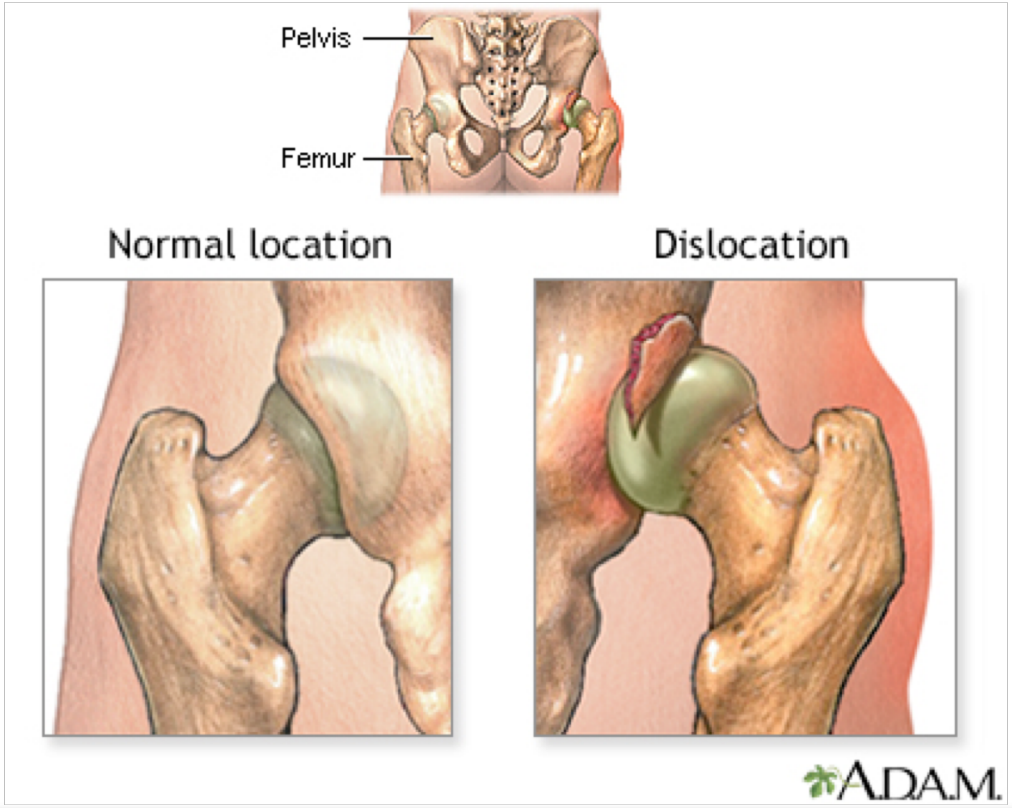




1. ADAM illustrations
2. https://www.med-ed.virginia.edu/courses/rad/chest/a08thoTension.html

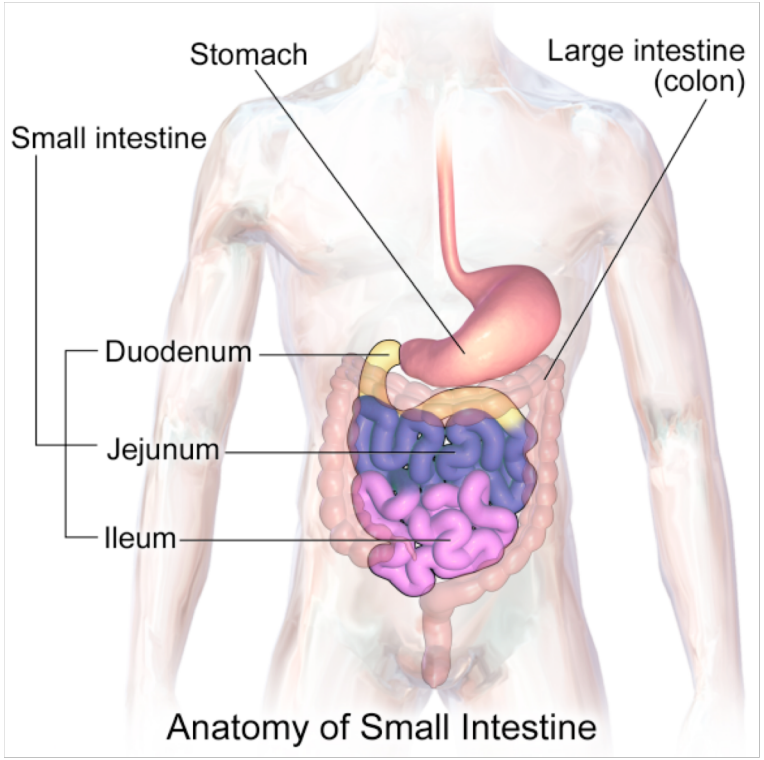
Complications – hernia, dislocations

- Inguinal (groin) hernia
- Recurrent joint subluxation or dislocation

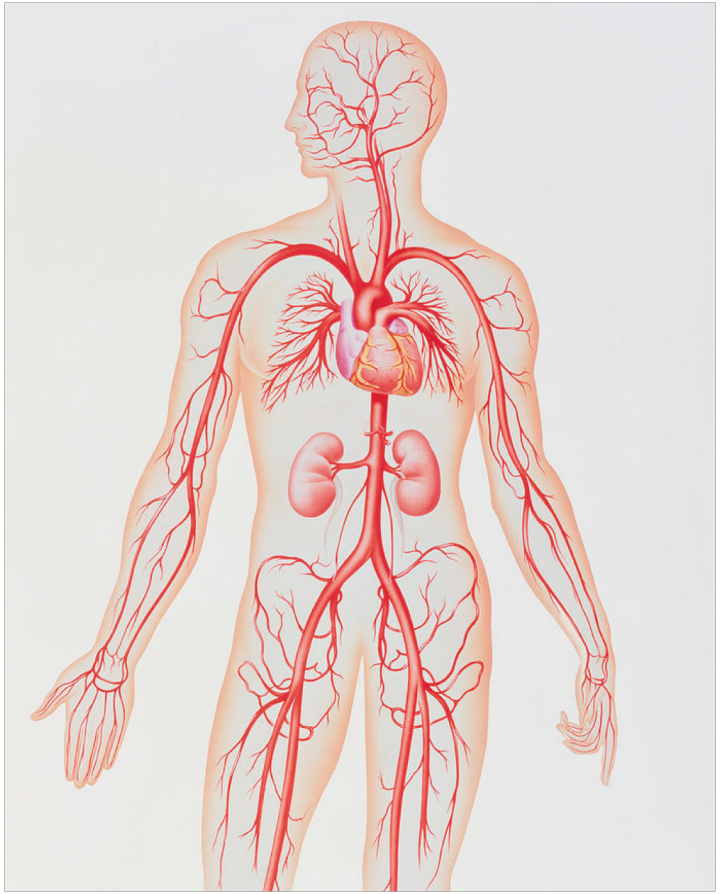


ADAM illustrations

Complications – intestinal rupture



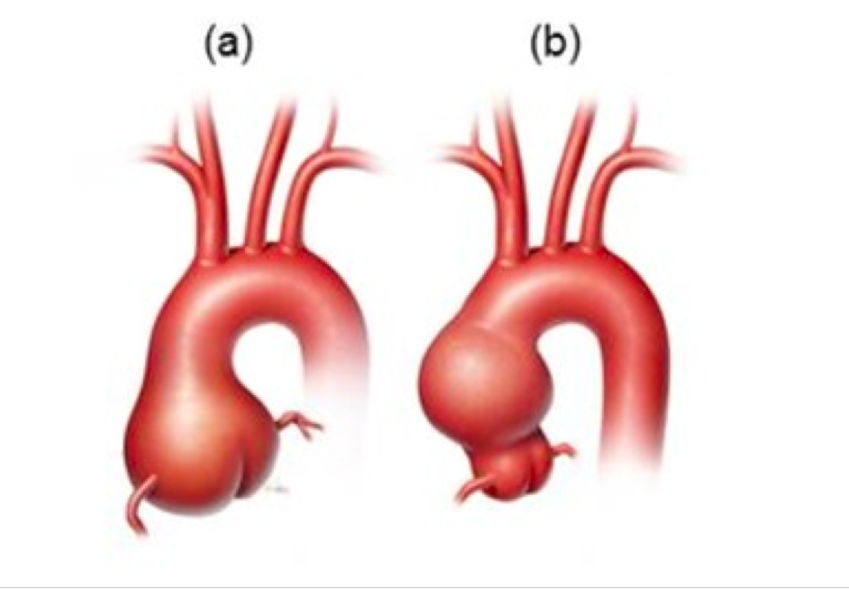
Complications – vascular aneurysm/dissection/rupture

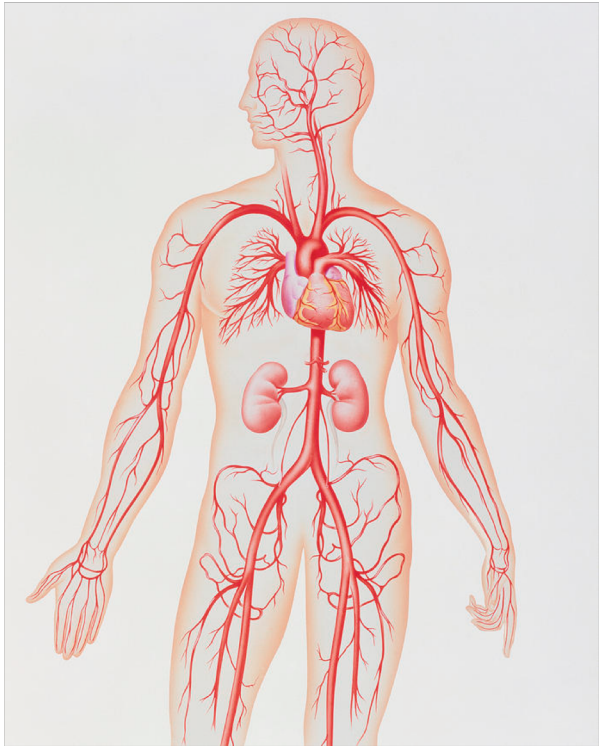


http://fineartamerica.com/featured/artwork-of-human-arterial-system-john-bavosi.html

Aortic/Arterial aneurysm vs. dissection vs. rupture

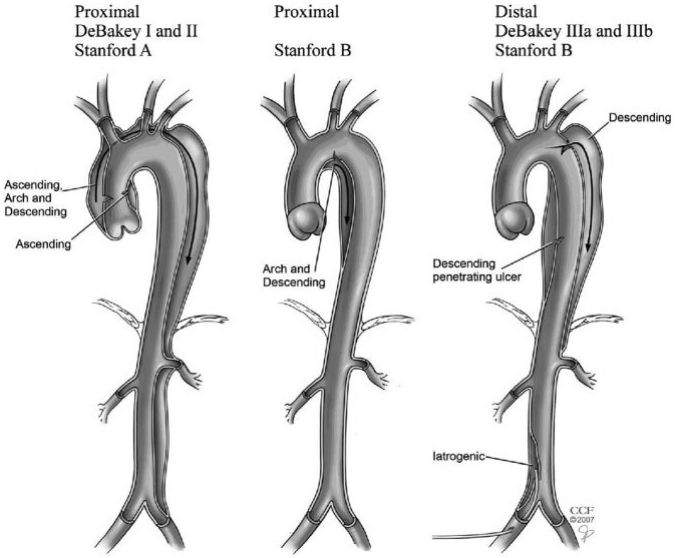
- Aneurysm: Dilation of part of a blood vessel

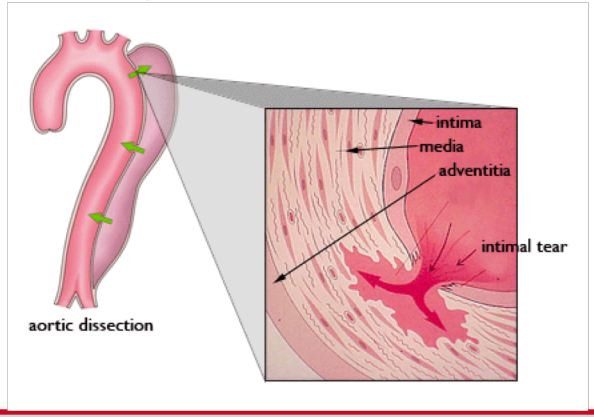




Aortic/Arterial aneurysm vs. dissection vs. rupture

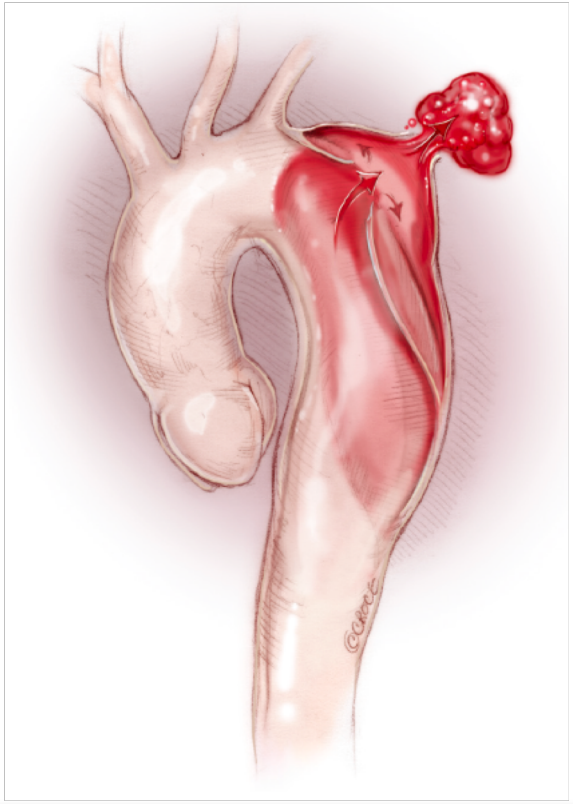
- Dissection:
  - Occurs when a tear of the intima (the inner lining) allows blood to leak into the media (middle layer).
  - This creates two passages for blood: a true lumen, which is the normal passageway of blood, and a false lumen, the newly created passageway.





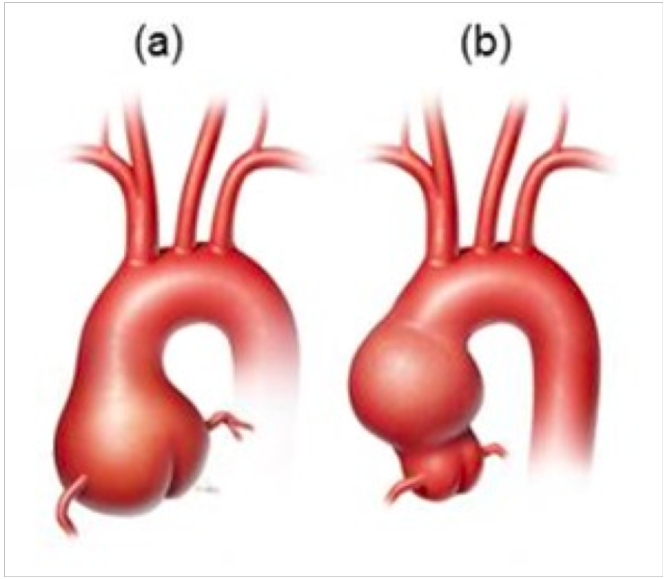
Aortic/Arterial aneurysm vs. dissection vs. rupture

- Rupture
  - Tearing of all three layers, allowing blood to leave the aorta/artery and the wall



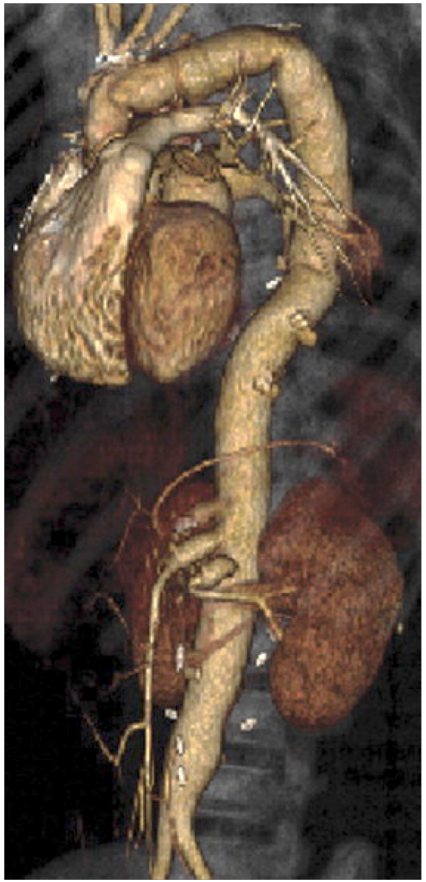
Aortic/arterial aneurysm in Vascular EDS

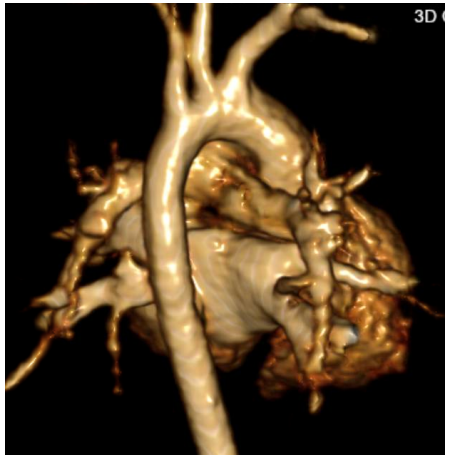
- In vEDS, most patients do not have the aortic root aneurysm seen in Marfan syndrome and Loeys-Dietz, or the ascending aortic aneursym seen in bicuspid aortic valve



Aortic Aneurysm/Dissection/Rupture in Vascular EDS

- Chest X-ray will NOT reliably pick up any of these
- Echo only images the aortic root well
- Must use:
  - Chest Computed Tomography/Cat scan/CT scan
  - Chest Magnetic Resonance Imaging/MRI/MRA



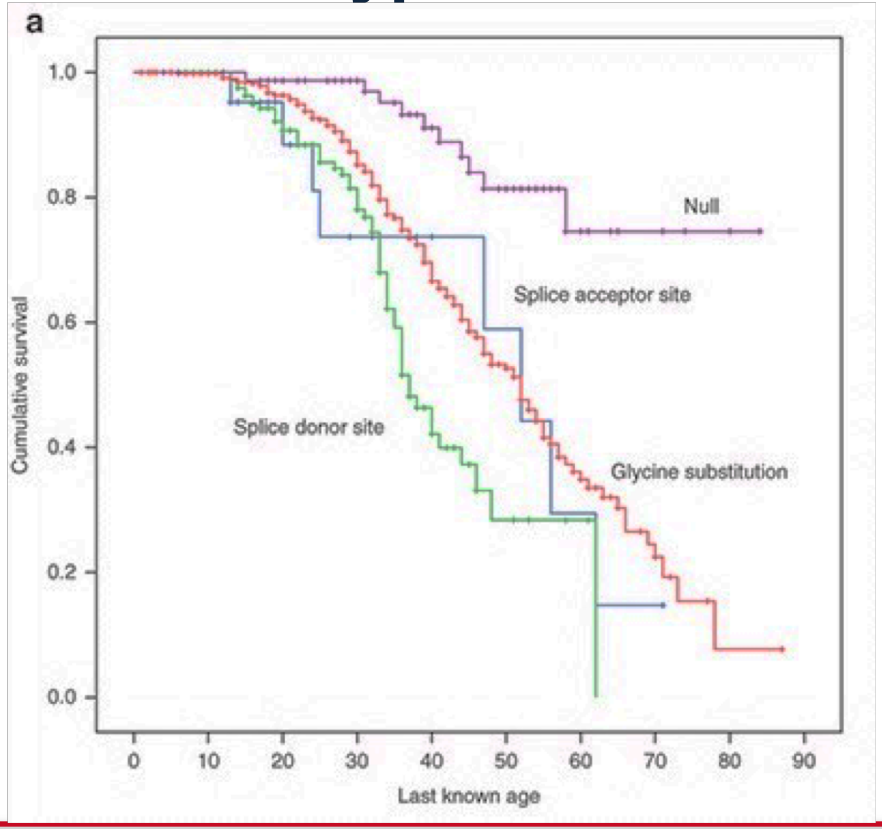


Can we predict the course?

- Specific mutation may matter (how it alters the Type III collagen)
  - If mutation results in <15% of expected levels
    - More likely to have gut/uterine involvement
    - Younger age at first event

Shalhub et al., J Vasc Surgery 2014

Survival by mutation type



Pepin et al., Genetics in Medicine 2014

Good news?

- Survival in children with Vascular EDS is high

Survival in Vascular EDS

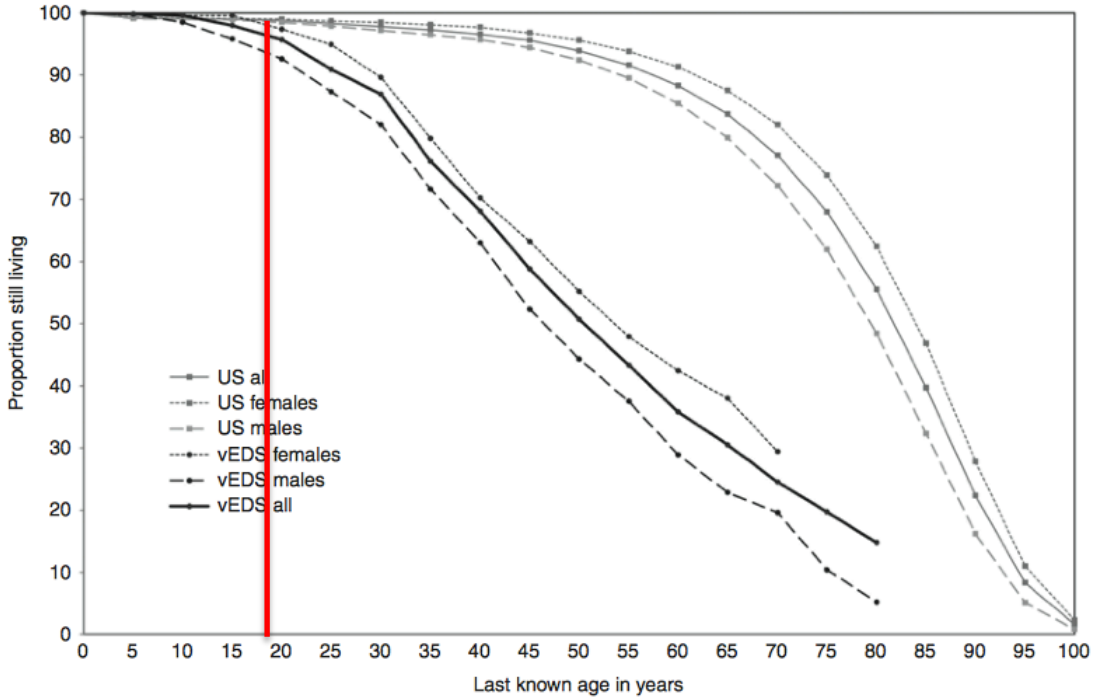


Figure 1 Kaplan–Meier survival curve comparing vascular Ehlers–Danlos syndrome (vEDS) study population to 2008 US population.

Pepin et al., Genetics in Medicine 2014

Good news-surgery in children

- Although surgery on the aorta and other vessels is difficult, it can be successful
  - 13 yo had multiple aortic surgeries for aortic aneurysms
  - 15 yo had successful repair after rupture of right subclavian artery (arm artery)
  - 13 yo had stent placed in artery to intestines after dissection, successful
  - 14 year old survived after near-lethal rupture of subclavian artery

Fukui et al., Annals of Thoracic Surgery 2014, Verbert et al., Acta Chir Belg 2013

Watching can work too

- Several examples of no intervention for dissection and later resolution
  - 12 yo boy with femoral (leg) artery dissection
  - Resolved with close medical and imaging follow up

Singh et al, Eur J Vasc Endovasc Surgery 2012

Clinical Trial

- 2010, study published in the Lancet

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

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

Clinical trial

- Studied celiprolol
  - Beta blocker (3rd generation)
  - Enrolled 53 patients in France and Belgium (8 centers) with vascular EDS, assigned them randomly to celiprolol or placebo
  - Ages 15-65 years
  - Medicine was increased in dose as tolerated
  - Followed for 5 years

Baylor College of Medicine

Texas Children's Hospital

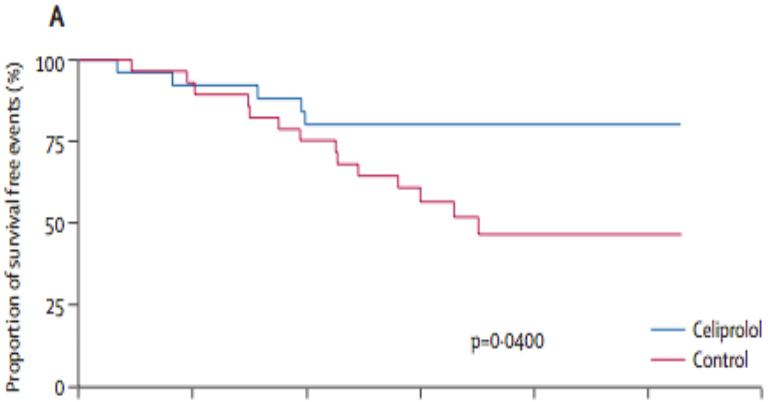
vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

THE MARFAN FOUNDATION

Clinical trial

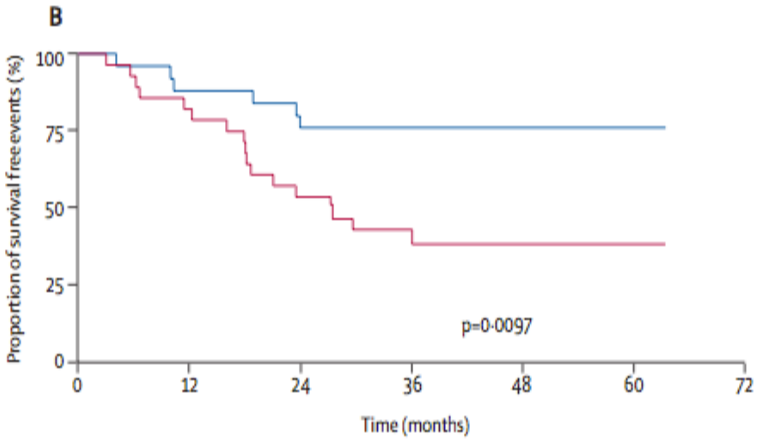
- Drug in 25 patients, 28 with no drug (placebo)
- Looked at how many patients in each group had dissection or rupture of an artery
- Drug: 5/25 (20%) had event
- Placebo: 14/28 (50%) had event

Freedom from Events



Number at risk/events

Celiprolol	25	24/2	21/5	16/5	13/5	5/5
Control	28	27/2	22/7	15/11	7/14	5/14



Number at risk/events

Celiprolol	25	23/3	20/6	16/6	13/6	5/6
Control	28	24/5	16/13	10/16	6/17	4/17

Baylor College of Medicine

Texas Children's Hospital®

vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

THE MARFAN FOUNDATION

Conclusions of study

- Celiprolol might be the treatment of choice for physicians aiming to prevent major complications in patients with vascular Ehlers-Danlos syndrome.

Our strategy at TCH

- Confirm genetic diagnosis
- Perform cascade screening (test relatives) if indicated
- Baseline head to pelvis imaging (usually MRA)
- Ensure families educated about risks and warning signs, emergency plans
- Activity limitations for older children
- Beta-blocker therapy, usually labetalol or carvedilol (other third generation beta-blockers)
- Serial imaging, depending on severity
- Minimize procedures. If needed, have a team prepared
- Connect family with other families

Baylor College of Medicine

Texas Children's Hospital

vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

THE MARFAN FOUNDATION

Summary

- Vascular EDS is rare, but very serious
- Caused by a problem with collagen formation
- Common features in children are thin, translucent skin, easy bruising, and aged hands and feet
- Most often picked up in children due to family history, easy bruising, clubfoot, hip dislocations, skin findings

Baylor College of Medicine

Texas Children's Hospital

vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

THE MARFAN FOUNDATION

Summary

- CT scan or MRI is best to evaluate for aneurysms, dissection, and rupture
- Knowing the diagnosis of vascular EDS significantly improved outcomes
- Surgery can be done if necessary
- Celiprolol, a beta blocker medication, may prevent adverse events in patients with vascular EDS

Baylor College of Medicine

Texas Children's Hospital

vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

THE MARFAN FOUNDATION

Baylor College of Medicine

Texas Children's Hospital®

vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

THE MARFAN FOUNDATION