SIMPOSIO ANNUALE DEL CENTRO
DI RIFERIMENTO PER LA SINDROME
DI MARFAN E PATOLOGIE CORRELATE
FOCUS SULLA SINDROME
DI EHLERS-DANLOS VASCOLARE

17 maggio 2025, ore 9:30-17:00
Aula Anfiteatro Giubileo 2000 - Policlinico Tor Vergata
Viale Oxford 81, 00133 - Roma

con il patrocinio di Fondazione Telethon

IL PRESENTE:
PRINCIPI DI PERSONALIZZAZIONE DELLE CURE DELLA PERSONA CON ARTERIOPATIA/AORTOPATIA EREDITARIA

Medicina personalizzata nelle arteriopatie/aortopatie ereditarie: applicazioni nella terapia farmacologica

Silvia Morlino, MD, PhD
UOC Genetica Medica
Fondazione IRCCS-Casa Sollievo della Sofferenza

FONDAZIONE
CASA SOLLIEVO DELLA SOFFERENZA
OPERA DI SAN PIO DA PIETRELCINA
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

RETE REGIONALE PER LE MALATTIE RARE

Unità coordinatrice: **UOC GENETICA MEDICA**

- **4795** certificati emessi (2011-2024) (>25% extra-regionali)
- **>140** codici ministeriali MR assegnati
- **14** UO coinvolte nella certificazione
- **14** ambulatori dedicati MR c/o CUP aziendale
- **1** sportello malattie rare (dal 2018)
- **1** ambulatorio malattie rare non diagnosticate

RETI INTERNAZIONALI

Rappresentante istituzionale:
UOC GENETICA MEDICA

European Reference Network | ERN ReCONNET

European Reference Networks | SKIN

The Ehlers Danlos Society

U.O.C. GENETICA MEDICA

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PERSONALE

- 4 Dirigenti Medici
- 5 Infermieri Professionali
- 10 Dirigenti Biologi
- 8 Tecnici Sanitari di Laboratorio Biomedico
- 1 Bioinformatico
- 1 Personale Amministrativo
- Personale di ricerca contrattista

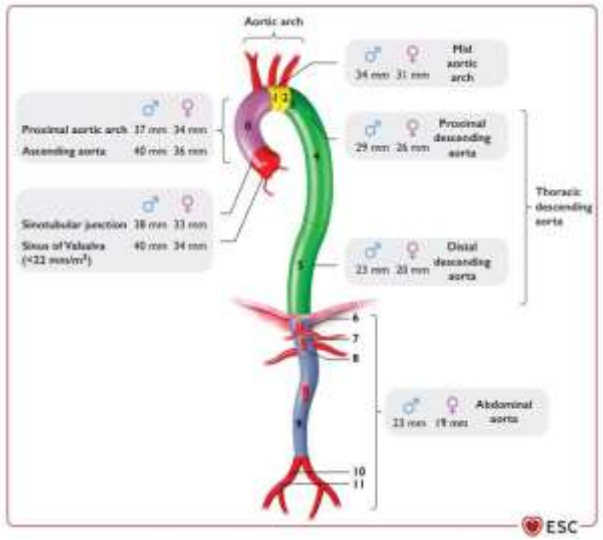
ATTIVITA'

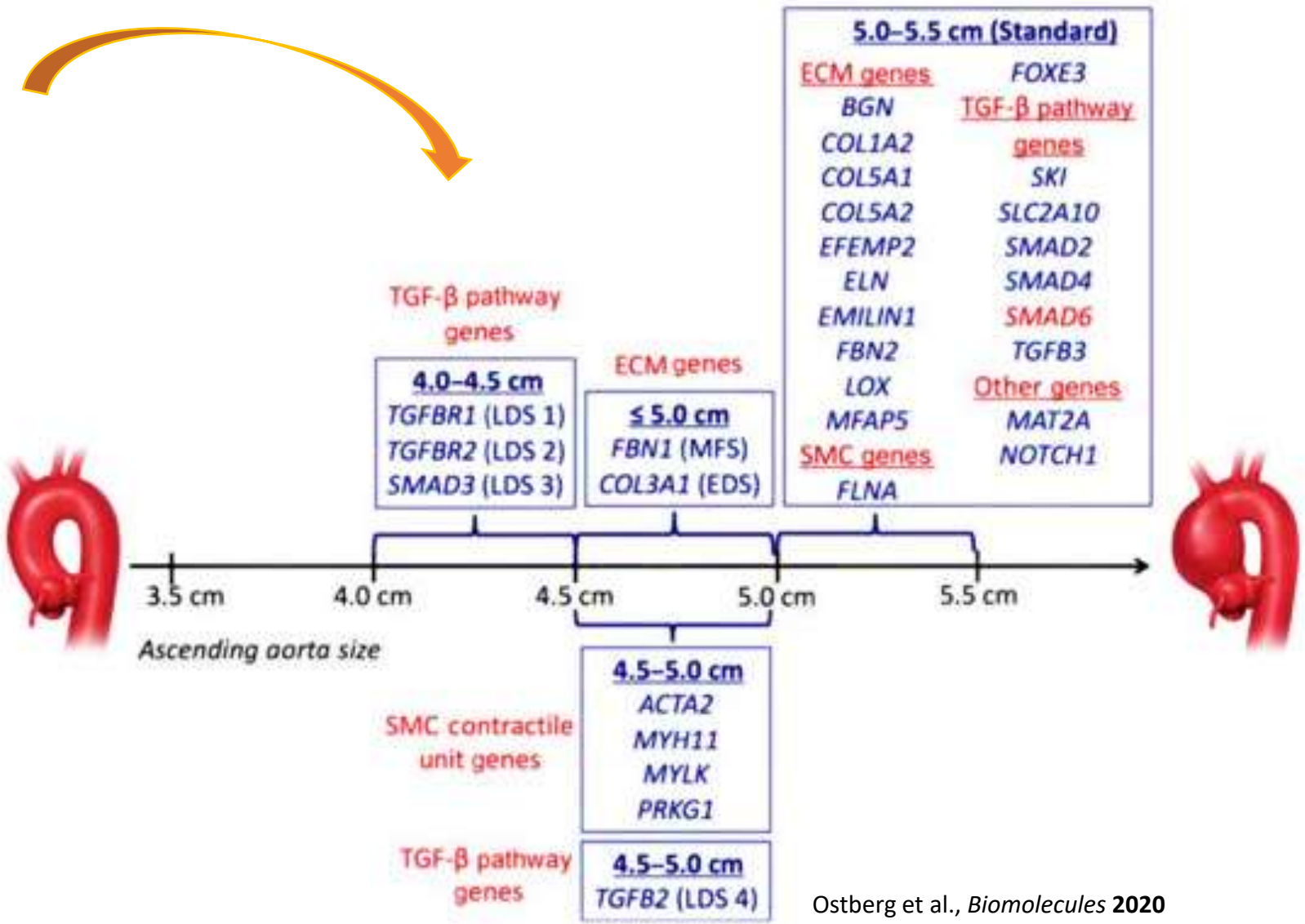
- Ambulatori malattie rare pediatrici, adulti e non diagnosticate
- Ambulatori cuore e vasi, neurosviluppo e oncogenetica
- Sportello malattie rare
- >2500 analisi NGS/anno
- >600 analisi SNParray e XONarray/anno

PROGETTI RICERCA (PI di progetto)

- Ricerca Finalizzata (RF-2021-12373524): multiOMICA nelle Malattie Rare
- PNRR (PNRR-MCNT2-2023-12377305): multiOMICA e bioinformatica in Cardiogenetica
- Telethon (GSA24J005): pre-clinica *vascular Ehlers-Danlos syndrome*

Hereditary Aortopathies





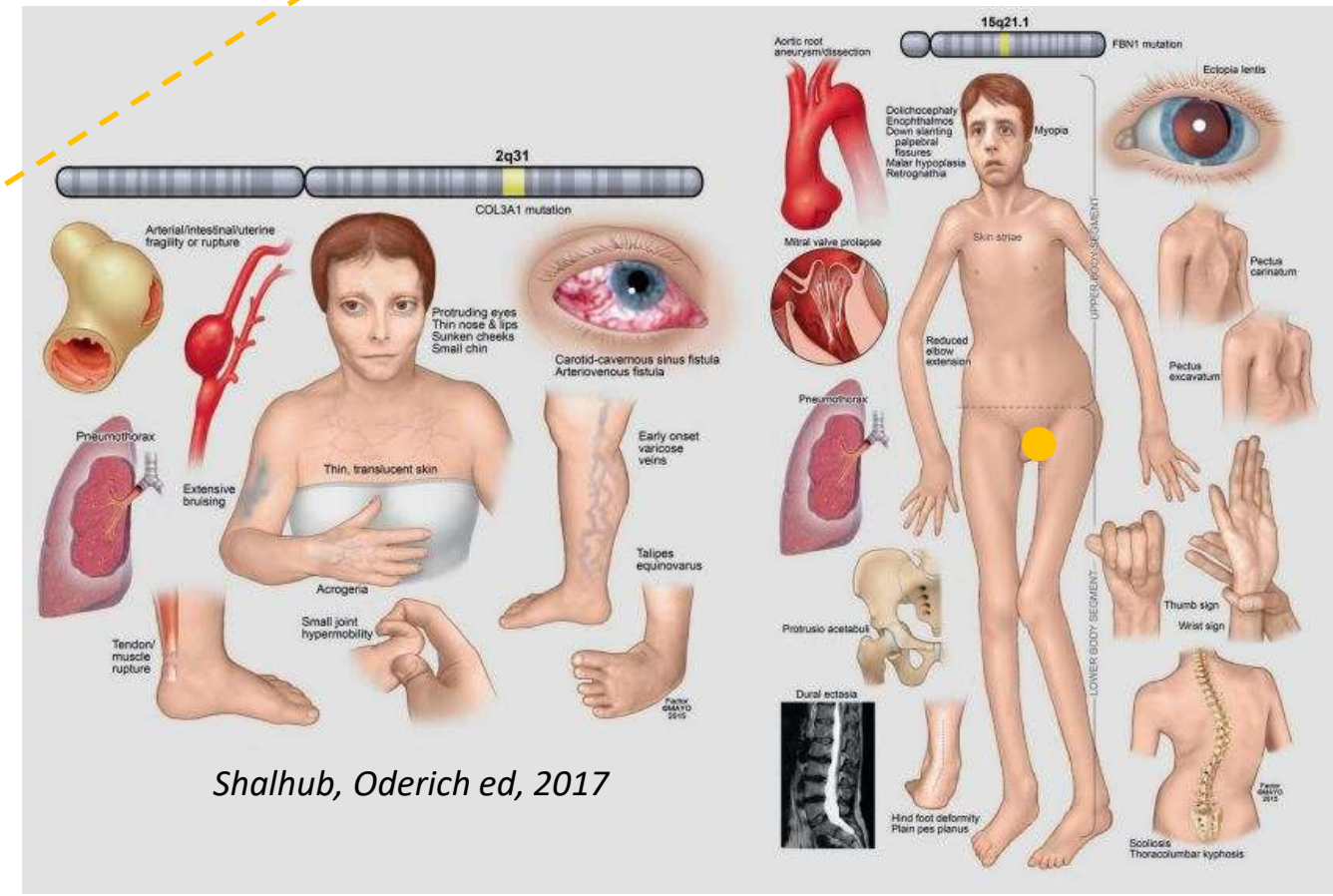
Ostberg et al., *Biomolecules* **2020**

Hereditary aortopathies and arteriopathies: Guidelines ESC 2024

Recommendations for medical treatment in patients with vascular Ehlers–Danlos syndrome
In patients with vEDS, regular vascular surveillance of the aorta and peripheral arteries by DUS, CCT, or CMR is recommended.
Treatment with celiprolol should be considered in patients with vEDS.
Recommendations for vascular imaging in Marfan syndrome
In patients with MFS, TTE is recommended: • At least annually in patients with an aortic root diameter <45 mm in the absence of additional risk factors • At least every 6 months in patients with an aortic root diameter <45 mm in the presence of additional risk factors • At least every 6–12 months in patients with an aortic root diameter ≥45 mm in the absence of additional risk factors
In patients without previous aortic surgery, complete peripheral vascular and thoracoabdominal aortic imaging by CMR or CCT and DUS is recommended at the first evaluation, and subsequently every 3–5 years if stable.
Recommendations for medical treatment in Marfan syndrome
In patients with MFS, treatment with either a BB or an ARB, in maximally tolerated doses (unless contraindicated), is recommended to reduce the rate of aortic dilatation.
In patients with MFS, the use of both a BB and an ARB, in maximally tolerated doses (unless contraindicated), should be considered to reduce the rate of aortic dilatation.
Recommendations for pregnancy in women with Marfan syndrome
It is recommended that all women with MFS: • Have a pre-conception evaluation to address the risks of maternal CV and other complications • Have follow-up in a centre with access to a pregnancy heart and vessel team
It is recommended that couples in which a partner has or is at risk of HTAD be offered pre-conception genetic counselling.
Imaging of the whole aorta (by CMR/CCT) is recommended prior to pregnancy.
Follow-up during pregnancy is recommended with a frequency determined by aortic diameter and growth.
Intake of BBs during pregnancy is recommended.
Prophylactic aortic root surgery is recommended in women desiring pregnancy with aortic diameters >45 mm.
Prophylactic aortic root surgery may be considered in women desiring pregnancy with aortic diameters of 40–45 mm.
Recommendations for physical exercise in patients with Marfan syndrome
It is recommended to individualize physical activity in patients with MFS based on aortic diameter, family history of aortic dissection, and pre-existing fitness.
Regular moderate aerobic exercise with a level of intensity informed by aortic diameter is recommended in most patients with MFS.
For patients who present with aortic dissection and/or have undergone aortic surgery, post-operative cardiac rehabilitation aiming at improving both physical and mental health should be considered.
Recommendations for imaging follow-up in Loeys–Dietz syndrome
In patients with Loeys–Dietz syndrome, TTE at baseline and subsequently every 6–12 months, depending on aortic diameter and growth, is recommended.
In patients with Loeys–Dietz syndrome, a baseline arterial imaging study from head to pelvis with CMR or CCT and subsequent surveillance with CMR or CCT or DUS every 1–3 years is recommended.
Recommendations for imaging and surgery in *ACTA2*-related heritable thoracic aortic disease
Annual monitoring of the aortic root/ascending aorta with TTE to evaluate for aortic root/ascending aorta enlargement is recommended.
Imaging of the aorta with CMR/CCT every 3–5 years is recommended.
Prophylactic aortic root surgery should be considered with a diameter ≥45 mm, or lower in cases with other risk factors.

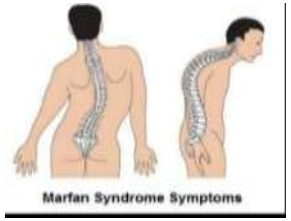
Vascular Ehlers-Danlos syndrome (vEDS)

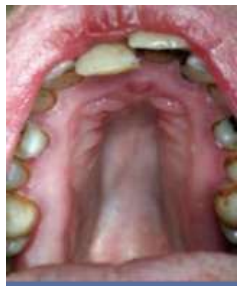
Marfan syndrome (MFS)

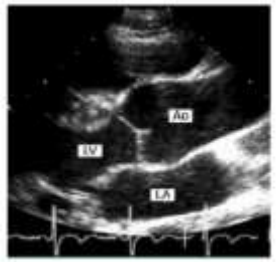


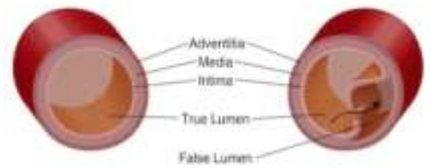
Shalhub, Oderich ed, 2017

Marfan Syndrome -MFS









Normal Dissected

FBN1 (MIM# 154700)

Incidence: 1:10.000

Ghent Nosology (2010)

CARDIOVASCULAR MANIFESTATIONS

- ✓ **Aortic root dilatation**
- ✓ **Aortic dissection**
- ✓ Mitral Valve Prolapse

OCULAR MANIFESTATIONS

- ✓ Ectopia lentis
- ✓ Myopia

OTHERS

- ✓ Pneumothorax

SKELETAL MANIFESTATIONS

- ✓ Dolichostenomelia
- ✓ Arachnodactyly
- ✓ Excavatum Pectus
- ✓ Scoliosis
- ✓ Joint hypermobility
- ✓ contractures
- ✓ Micrognathia
- ✓ High arched palate

Recommendations for medical treatment in Marfan syndrome
In patients with MFS, treatment with either a BB or an ARB, in maximally tolerated doses (unless contraindicated), is recommended to reduce the rate of aortic dilatation.
In patients with MFS, the use of both a BB and an ARB, in maximally tolerated doses (unless contraindicated), should be considered to reduce the rate of aortic dilatation.

Recommendation Table 61 — Recommendations for medical treatment in Marfan syndrome (see also Evidence Table 14)

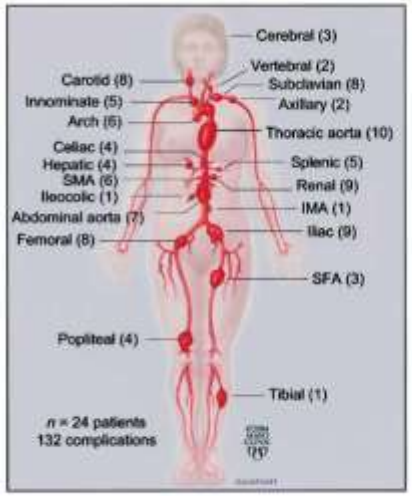
Recommendations	Class[a]	Level[b]
In patients with MFS, treatment with either a BB or an ARB, in maximally tolerated doses (unless contraindicated), is recommended to reduce the rate of aortic dilatation.[1461,1462]	I	A
In patients with MFS, the use of both a BB and an ARB, in maximally tolerated doses (unless contraindicated), should be considered to reduce the rate of aortic dilatation.[1463,1464]	IIa	A

ARB, angiotensin receptor blocker; BB, beta-blocker; MFS, Marfan syndrome.
[a]Class of recommendation.
[b]Level of evidence.

Vascular Ehlers Danlos syndrome - vEDS

COL3A1 (MIM#130050)

Estimated prevalence of 1/20,000-150,000

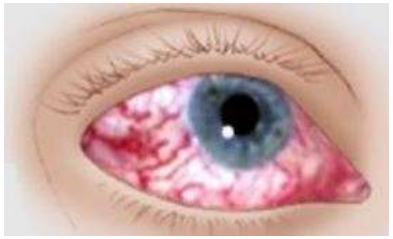


Oderich et al, Journal of Vascular Surgery, 2005

For Ehlers-Danlos syndromes (EDS) we intend a clinically and genetically heterogeneous group of heritable connective tissue disorders mainly featuring joint hypermobility, abnormal cutaneous texture, easy bruising, and tissue fragility, according to **2017 EDS classification (Malfait et al., 2017).**

❑ vEDS is the most severe clinical form of EDS, characterized by:

- **rupture of arteries,** gravid uterus
- bowel perforation
- **aortic dissection**
- characteristic facial appearance
- easy bruising, difficult scarring
- **artero-venous fistula** (*carotid cavernous fistula*)
- translucent skin, acrogeria
- pneumothorax (dd MFS)

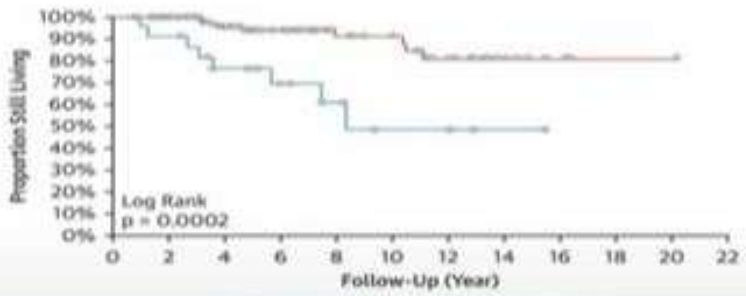


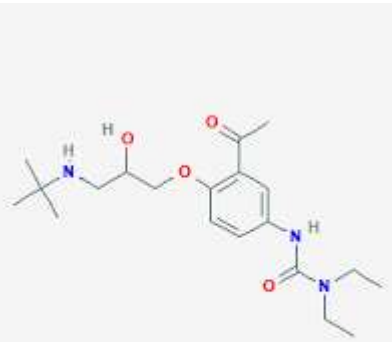
❑ vEDS is caused by heterozygous deleterious variants in the *COL3A1* gene that encodes the pro-alfa1 chain of type III procollagen (Collagen III, COLLIII), a major fibrillar collagen in the ECM that is highly expressed in soft tissues with elastic properties including dermis, blood vessels, and gastro-intestinal tract

Shalhub et al, Journal of Vascular Surgery, July 2014

vEDS – pharmacological resources

- How to reduce life-threatening vascular events and to increase life expectancy?
  - Medical intervention is destined to maintain blood pressure within a normal range and to avoid surges in blood pressure that may increase risk of arterial events
  - A variety of cardiovascular medications is available for that purpose
  - To date, only one clinical trial has systematically addressed reduction of arterial events with a mixed β1 antagonist and β2 agonist, celiprolol with promising results



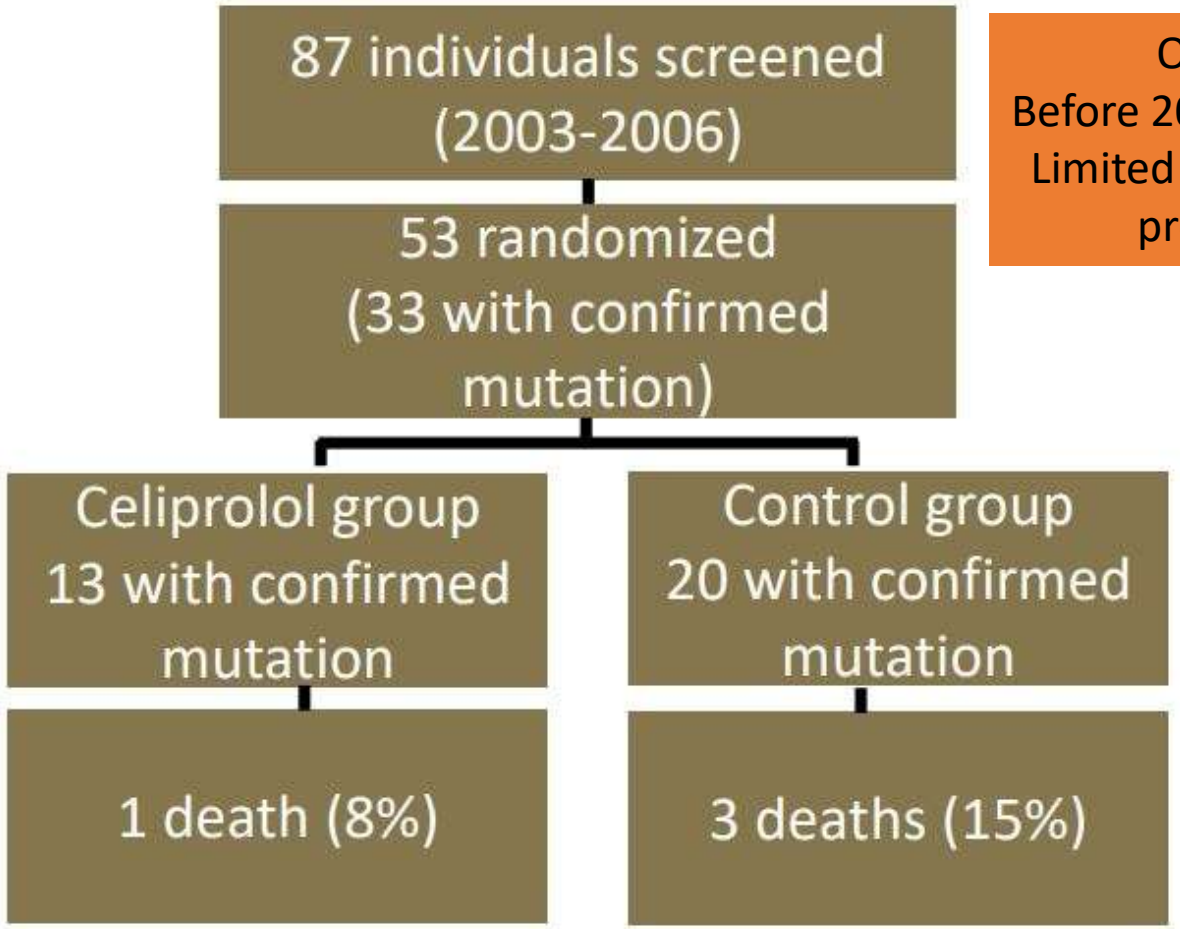


Lancet; 2010: celiprolol therapy for vascular EDS

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



Open trial
Before 2017 classification
Limited no. molecularly proven vEDS

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
	rol	Spontaneous cerebral hematoma
	rol	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)

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Vascular Ehlers-Danlos Syndrome

Long-Term Observational Study

Michael Frank, MD,[a,b] Salma Adham, MD,[a,c] Stéphanie Seigle, MSc,[a] Anne Legrand, PharmD,[a,b,c] Tristan Mirault, MD, PhD,[a,d] Pierrick Henneton, MD,[a,e] Juliette Albuisson, MD, PhD,[a,b,c] Nicolas Denarié, MD,[a] Jean-Michaël Mazzella, MSc,[a] Elie Mousseaux, MD, PhD,[b,c,f] Emmanuel Messas, MD, PhD,[a,d] Pierre Boutouyrie, MD, PhD,[b,c,g] Xavier Jeunemaitre, MD, PhD[a,b,c]

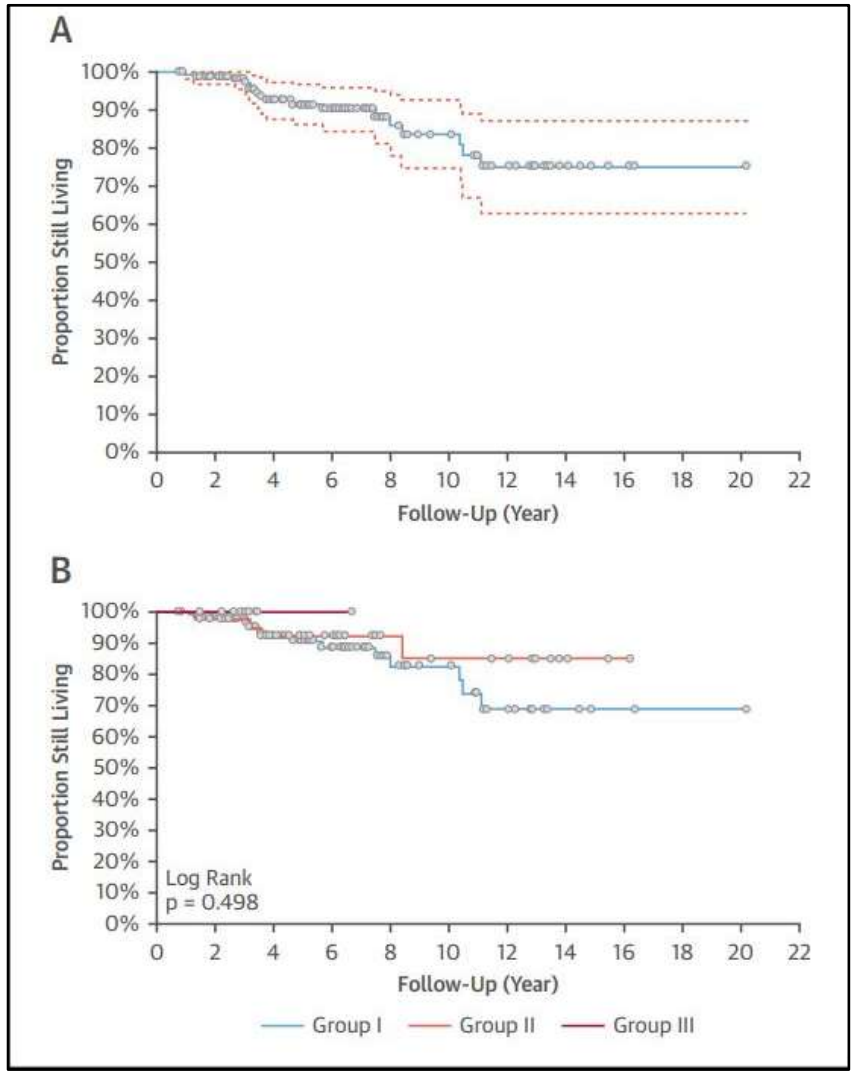
144 vEDS patients
(2000-2017)

Monocentric
Restrospective
observational study
Absence of control group

91 index cases
53 relatives
90 Gly-change variants (Gr I)
42 splice-site variants (Gr II)
12 haploinsufficiency variants (Gr III)

107 arterial events
in 52 patients (39,4%, GrI Gr II)

17 vEDS patients
died (11,8%)
12 arterial rupture (71%)
2 gastrointestinal perforation (12%)
3 unrelated to vEDS, 0 GrIII



(A) Overall vascular Ehlers-Danlos syndrome (vEDS) patient survival since molecular diagnosis. Patient survival was 99.3% at year 1, 89.9% at year 5, and 83.4% at year 10 of follow-up. Overall patient survival was 74.9% (95% confidence interval [CI]: 62.7% to 87.0%) after 11.1 years of follow-up. **(B)** Survival according to the type of *COL3A1* pathogenic variant. Patient survival did not significantly differ between groups of pathogenic variants (Group I: 68.7% [95% CI: 51.9% to 85.5%] vs. Group II: 84.8% [95% CI: 69.2% to 100%] vs. Group III: 100%). Log-rank (Group I vs. Group II vs. Group III) $p = 0.498$.

Original Research Article

VASCULAR MEDICINE

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2024, Vol. 29(3) 265–273
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Sage

Despite celiprolol therapy, patients with vascular Ehlers–Danlos syndrome remain at risk of vascular events: A 12-year experience in an Italian referral center

Giacomo Buso[1,2], Anna Paini[1], Claudia Agabiti-Rosei[1], Carolina De Ciuceis[1], Fabio Bertacchini[1], Deborah Stassaldi[1], Massimo Salvetti[1], Marco Ritelli[3], Marina Venturini[4], Marina Colombi[3] and Maria Lorenza Muiesan[1]

2024

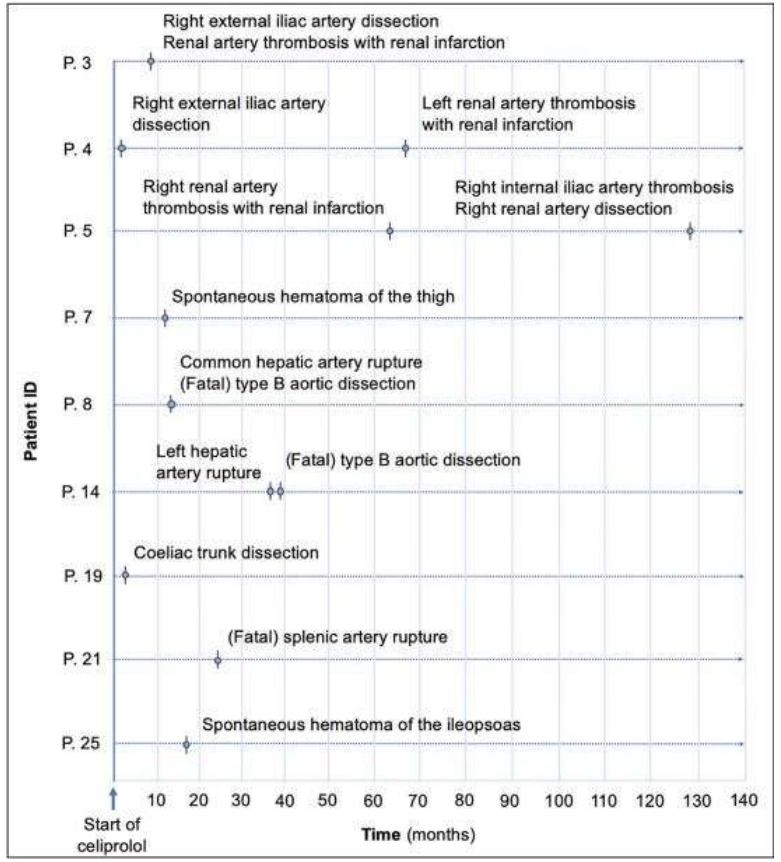
26 vEDS patients
(2011-2023)

19 index cases
7 relatives
13 Gly-change variants
4 splice-site variants
1 haploinsufficiency variants

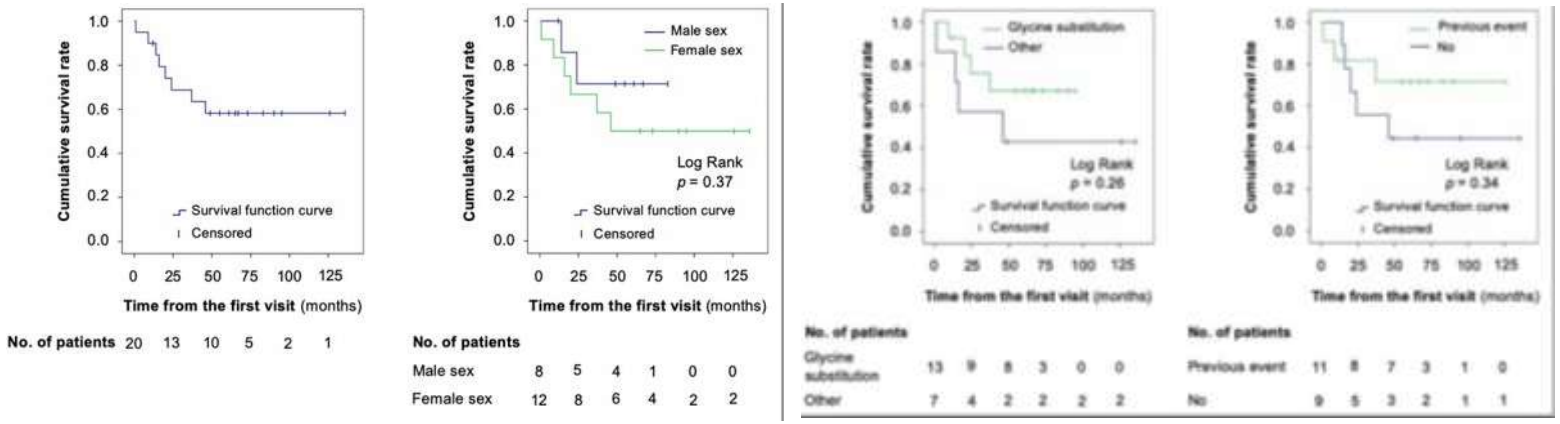
3 fatal events (15 yo, 37 yo,42 yo)
during celiprolol therapy

18 total clinical events (14,4% yearly risk)
12 vascular events (11 symptomatic events)
14 vEDS patients with 1 or more
major events in follow-up
10/18 vascular events after reaching 400 mg/die dose

Monocentric
observational study
Absence of control group



Symptomatic vascular events during celiprolol therapy



Survival function (Kaplan-Meier) of symptomatic vascular events (tot, sex, genotype, previous events)

ESC European Society of Cardiology
European Heart Journal (2024) **45**, 3538–3700
https://doi.org/10.1093/eurheartj/ehae179

2024 ESC Guidelines for the management of peripheral arterial and aortic diseases

Developed by the task force on the management of peripheral arterial and aortic diseases of the European Society of Cardiology (ESC)

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS), the European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN), and the European Society of Vascular Medicine (ESVM)

Authors/Task Force Members: Lucia Mazzolai *†, (Chairperson) (Switzerland), Gisela Teixido-Tura ‡, (Task Force Co-ordinator) (Spain), Stefano Lanzi ‡, (Task Force Co-ordinator) (Switzerland), Vinko Boc (Slovenia), Eduardo Bossone (Italy), Marianne Brodmann [1] (Austria), Alessandra Bura-Rivière (France), Julie De Backer [2] (Belgium), Sebastien Deglise (Switzerland), Alessandro Della Corte (Italy), Christian Heiss (United Kingdom), Marta Kałużna-Oleksy (Poland), Donata Kurpas (Poland), Carmel M. McEniery (United Kingdom), Tristan Mirault (France), Agnes A. Pasquet (Belgium), Alex Pitcher (United Kingdom), Hannah A.I. Schaubroeck (Belgium), Oliver Schlager (Austria), Per Anton Sirnes (Norway), Muriel G. Sprynger (Belgium), Eugenio Stabile (Italy), Françoise Steinbach (France), Matthias Thielmann (Germany), Roland R.J. van Kimmenade (Netherlands), Maarit Venermo (Finland), Jose F. Rodriguez-Palomares *†, (Chairperson) (Spain), and ESC Scientific Document Group

Recommendation Table 59 — Recommendations for medical treatment in patients with vascular Ehlers–Danlos syndrome (see also Evidence Table 13)

Recommendations	Class[a]	Level[b]
In patients with vEDS, regular vascular surveillance of the aorta and peripheral arteries by DUS, CCT, or CMR is recommended.[1439,1443]	I	C
Treatment with celiprolol should be considered in patients with vEDS.[1441,1444,1445]	IIa	B

CCT, cardiovascular computed tomography; CMR, cardiovascular magnetic resonance; DUS, duplex ultrasound; vEDS, vascular Ehlers–Danlos syndrome.
[a]Class of recommendation.
[b]Level of evidence.

10.1.2. Vascular Ehlers–Danlos syndrome

10.1.2.1. Diagnosis, clinical presentation, and natural history

Vascular Ehlers–Danlos syndrome is a rare (prevalence of 1/50 000 to 1/200 000) autosomal dominant disease caused by pathogenic variants in the *COL3A1* gene, which encodes the pro-alpha1 chains of type III procollagen. The most common *COL3A1* variants provoke a disruption in the assembly of type III collagen fibrils, causing an important loss of mechanical strength of arteries and other hollow organs, especially the bowel and uterus.[1438] Identification of a causal *COL3A1* variant is a requirement for the diagnosis of vEDS.[1439]

vEDS is the most severe form of Ehlers–Danlos syndrome because of its clinical life-threatening vascular complications, making early identification and a thorough family inquiry particularly crucial.

Clinical complications may start during adolescence and repeat at unpredictable time intervals. The most common complications involve medium-sized arteries: dissections, aneurysms, arterial ruptures, and arteriovenous fistulas. AD (both type A and B) occurs in up to 10% of patients.[1440]

Prognosis depends on the type of *COL3A1* variant, with null variants (no gene product or absence of function) showing a better outcome.[1441] The rate of recurrence of organic complications in patients with vEDS is 1.6 events per 5 year period. Life expectancy is reduced to an average of 51 years.[1442]

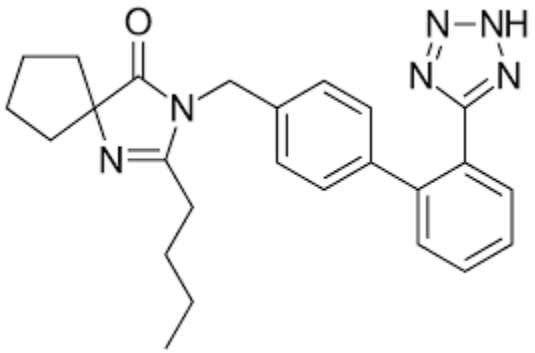
10.1.2.2. Surveillance and imaging

Management of vEDS is complex and requires a multidisciplinary approach. Recommendations include: lifestyle modification to minimize injury and risk of vessel/organ rupture, identification of a care team, individualized emergency care plans, maintaining BP in the normal range, aggressive hypertension treatment, and annual surveillance of the vascular tree by DUS, CCT (low radiation alternatives), or CMR (if feasible).[1439] A recent survey among European expert centres indicated that arterial monitoring is standard clinical practice and that frequency of follow-up should be adapted individually.[1443] The prognosis improves when patients are properly managed.[1441]

10.1.2.3. Medical treatment

Medical management is based on optimal BP control. Celiprolol, a BB with vasodilatory properties, has been shown to reduce vascular morbidity in two retrospective studies[1441,1444] and one randomized, open-label trial.[1445] There is no consensus about the age at which to start treatment, but starting after 10 years of age is considered reasonable by many experts.

vEDS – polytherapy?



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Circulation

RESEARCH ARTICLE | Originally Published 5 February 2025

Efficacy of Irbesartan in Celiprolol-Treated Patients With Vascular Ehlers-Danlos Syndrome

Xavier Jeunemaitre, MD, PhD, Elie Mousseaux, MD, PhD, Michael Frank, MD, Salma Adham, MD, Francesca Pitocco, MD, Clarisse Billon, PharmaD, Molka Ben Yakhlef, MD, ... SHOW ALL ..., and Michel Azizi, MD, PhD AUTHOR INFO & AFFILIATIONS

Circulation • Volume 151, Number 10 • https://doi.org/10.1161/CIRCULATIONAHA.124.072849

https://www.clinicaltrials.gov/study/NCT02597361?cond=NCT02597361&rank=1#locations

Multicenter, randomized, placebo-controlled trial

- **irbesartan (150 mg/day titrated to 300 mg/day) or placebo for 2 years**.
- outcome →any vascular Ehlers-Danlos syndrome–related **fatal or nonfatal arterial event** or any new or **worsening arterial lesions** detected by systematic head-to-pelvis CTA or peripheral arterial duplex ultrasound at different time points, using a time-to-first-event analysis.
- **29 vEDS patients** (62% female; 40.3±11.3 years of age) →**irbesartan.**
- **28 vEDS patients** (64% female; 40.7±11.0 years of age) →**placebo**.
- The composite primary outcome occurred in 8 of 29 patients (**27.6%**) receiving irbesartan versus 15 of 28 patients (**53.6%**) receiving placebo (hazard ratio, 0.42 [95% CI, 0.17, 0.99]; *P*<0.05).
- The risk of recurrent **symptomatic** or **nonsymptomatic** arterial events was **lower** with irbesartan than with placebo (risk ratio, **0.37** [95% CI, 0.19, 0.68]; *P*=0.002).
- A reduction of progression of arterial lesions was observed at all sites.
- **11 episodes** of irbesartan-related **hypotension** were recorded, leading to a downtitration in **4 patients**.

Compared with placebo, irbesartan reduced the risk of severe symptomatic and asymptomatic arterial events in patients with vascular Ehlers-Danlos syndrome on background celiprolol therapy.

Drugs to avoid

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scientific reports

2024

OPEN

The association between fluoroquinolones and aortic dissection and aortic aneurysms: a systematic review and meta-analysis

Ian Wee[1,2], Brian Chin[1,2], Nicholas Syn[1,2], Keng Siang Lee[1,3], Jun Jie Ng[1,3,4] & Andrew M. T. L. Choong[1,3,4,5]

Previous studies have drawn causal associations between fluoroquinolone use and collagen pathologies including tendon rupture and retinopathy. This meta-analysis attempted to assess the association between fluoroquinolone use and the risk of aortic dissection or aortic aneurysm. A systematic search was performed on Medline, EMBASE, and the Cochrane library. 9 studies were included in final analysis. Primary random-effects meta-analysis of 7 studies, excluding 2 pharmacovigilance studies demonstrated statistically increased odds of aortic dissection (OR, 2.38; 95% CI, 1.71–3.32) aortic aneurysm (OR, 1.98; 95% CI, 1.59–2.48), and aortic aneurysm or dissection (OR, 1.47; 95% CI, 1.13–1.89; I^2 = 72%) with current use of fluoroquinolones compared to their nonuser counterparts. Based on the "number needed-to-harm" analysis, 7246 (95% CI: 4329 to 14,085) patients would need to be treated with fluoroquinolones for a duration of at least three days in order for one additional patient to be harmed, assuming a population baseline incidence of aortic dissection and aneurysm rupture to be 10 per 100,000 patient-years. With strong statistical association, these findings suggest a causal relationship, warranting future research to elucidate the pathophysiological and mechanistic plausibility of this association. These findings however, should not cease prescription of fluoroquinolones, especially when clinically indicated.

JAMA Network — Click to view article >

• JAMA Surg. 2021 Jan 6;156(3):264–272. doi: 10.1001/jamasurg.2020.6165

Association of Fluoroquinolone Use With Short-term Risk of Development of Aortic Aneurysm

Emily R Newton [1], Adam W Akerman [1], Paula D Strassle [1], Melina R Kibbe [1,2,3,✉]

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PMCID: PMC7788511 PMID: 33404647

• JAMA Cardiol. 2023 Aug 16;8(9):865–870. doi: 10.1001/jamacardio.2023.2418

Association Between Fluoroquinolone Use and Hospitalization With Aortic Aneurysm or Aortic Dissection

Jeremy P Brown [1,✉], Kevin Wing [1], Clémence Leyrat [1,2], Stephen J Evans [2], Kathryn E Mansfield [1], Angel Y S Wong [1], Liam Smeeth [1], Nicholas W Galwey [3], Ian J Douglas [1]

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NOTA INFORMATIVA IMPORTANTE CONCORDATA CON LE AUTORITA' REGOLATORIE EUROPEE E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

Ottobre 2018

Fluorochinoloni ad uso sistemico ed inalatorio: rischio di aneurisma e dissezione dell'aorta

Gentile Dottoressa/Egregio Dottore,

I titolari di specialità medicinali contenenti fluorochinoloni (ciprofloxacina - levofloxacina - moxifloxacina - pefloxacina - prulifloxacina - rufloxacina - norfloxacina - lomefloxacina) in accordo con l'Agenzia Europea dei Medicinali (EMA) e l'Agenzia Italiana del Farmaco (AIFA), desiderano informarLa dell'introduzione di una nuova avvertenza riguardante il rischio di aneurisma e dissezione dell'aorta associato a fluorochinoloni per uso sistemico e inalatorio.

Riassunto

- **I fluorochinoloni per uso sistemico e inalatorio possono aumentare il rischio di aneurisma e dissezione dell'aorta, in particolare nelle persone anziane.**
- **Nei pazienti a rischio di aneurisma e dissezione dell'aorta, i fluorochinoloni devono essere utilizzati solo dopo un'attenta valutazione del rapporto beneficio/rischio e dopo aver preso in considerazione altre opzioni terapeutiche.**
- **Le condizioni che predispongono all'aneurisma e alla dissezione dell'aorta comprendono una storia familiare di aneurisma, aneurisma aortico o dissezione aortica pre-esistente, sindrome di Marfan, sindrome vascolare di Ehlers-Danlos, arterite di Takayasu, arterite a cellule giganti, malattia di Behçet, ipertensione e aterosclerosi.**
- **I pazienti devono essere allertati del rischio di aneurisma e dissezione dell'aorta e devono essere invitati a cercare assistenza medica immediata in pronto soccorso in caso di improvviso e severo dolore addominale, toracico o alla schiena.**

Nutritional resources

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DOI: 10.1111/hae.15099

2024

Haemophilia WFH WILEY

ORIGINAL ARTICLE
Rare bleeding disorders

Low vitamin C status and hypermobility-related disorders in patients with bleeding disorder of unknown cause

Eva Leinøe[1,2] | Halla Fridriksdottir[1] | Andreas Ørslev Rasmussen[2] | Eva Funding[1,3] | Anne Louise Tølbøll Sørensen[1] | Peter Kampmann[1] | Jens Lykkesfeldt[4] | Maria Rossing[2,3]

positive BS in 29/60 patients compared to 1/20 healthy controls (HC) ($p < .001$).

10/60 patients met the clinical diagnostic criteria for hEDS, and 1/60 patient was diagnosed with Noonan syndrome.

Case Reports > Adv Skin Wound Care. 2021 Jul 1;34(7):1-6.
doi: 10.1097/01.ASW.0000741524.79369.7a.

Vascular Ehlers-Danlos Syndrome: Treatment of a Complex Abdominal Wound with Vitamin C and Mesenchymal Stromal Cells

David Andrew Prentice [1], Wendy Ann Pearson, Janice Fogarty

Affiliations + expand

PMID: 33851936 DOI: 10.1097/01.ASW.0000741524.79369.7a

Medical Hypotheses (2005) 64, 279–283

ELSEVIER

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

A novel therapeutic strategy for Ehlers–Danlos syndrome based on nutritional supplements

D. Mantle[a,*], R.M. Wilkins[b], V. Preedy[c]

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Healthy Lifestyle

cells

MDPI

Review

Mitochondrial DNA and Exercise: Implications for Health and Injuries in Sports

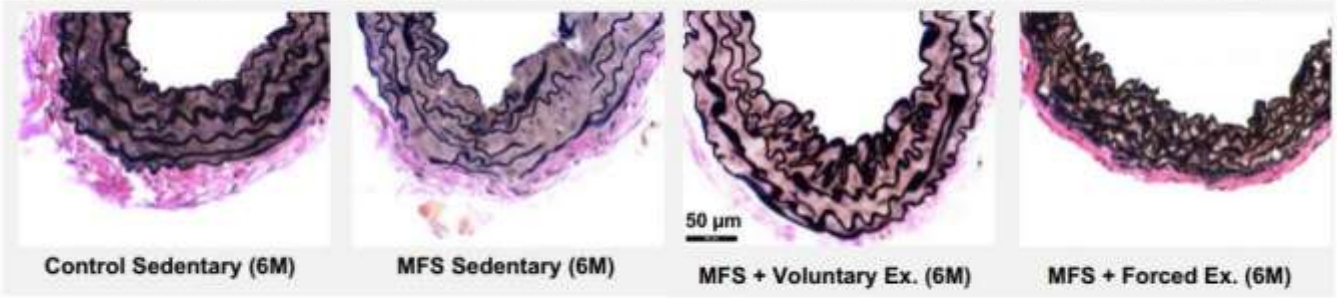
Giada Zanini [1], Anna De Gaetano [1,2], Valentina Selleri [1], Gustavo Savino [3], Andrea Cossarizza [2,4], Marcello Pinti [1], Anna Vittoria Mattioli [2,5,†] and Milena Nasi [5,*,†]

RESEARCH ARTICLE

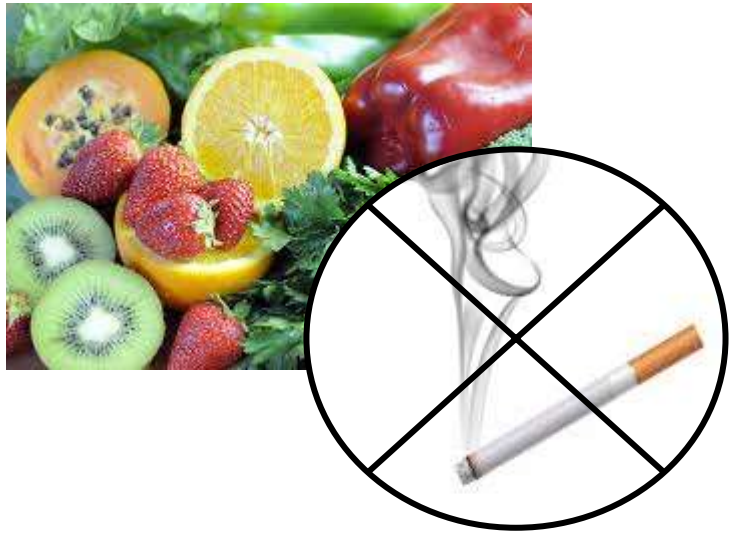
J Appl Physiol 123: 147–160, 2017.
First published April 6, 2017; doi:10.1152/japplphysiol.00132.2017.

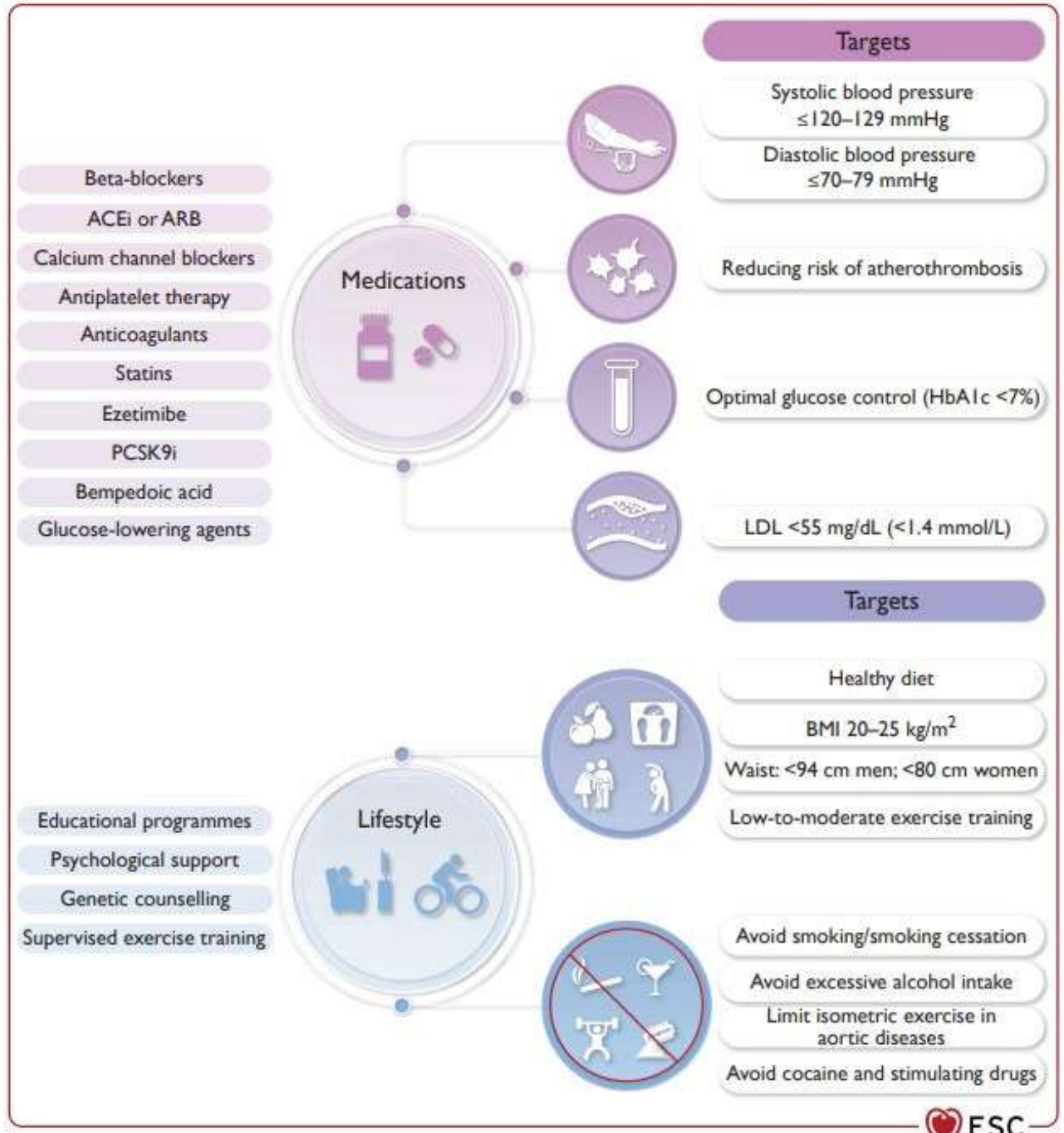
Mild aerobic exercise blocks elastin fiber fragmentation and aortic dilatation in a mouse model of Marfan syndrome associated aortic aneurysm

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)




Targets
Systolic blood pressure ≤120–129 mmHg
Diastolic blood pressure ≤70–79 mmHg
Beta-blockers
ACEi or ARB
Calcium channel blockers
Antiplatelet therapy
Anticoagulants
Statins
Ezetimibe
PCSK9i
Bempedoic acid
Glucose-lowering agents
Medications
Reducing risk of atherothrombosis
Optimal glucose control (HbA1c <7%)
LDL <55 mg/dL (<1.4 mmol/L)
Targets
Healthy diet
BMI 20–25 kg/m2
Waist: <94 cm men; <80 cm women
Low-to-moderate exercise training
Educational programmes
Psychological support
Genetic counselling
Supervised exercise training
Lifestyle
Avoid smoking/smoking cessation
Avoid excessive alcohol intake
Limit isometric exercise in aortic diseases
Avoid cocaine and stimulating drugs
ESC

looking for clinically valid biomarkers

› Hypertens Res. 2025 Apr;48(4):1529-1541. doi: 10.1038/s41440-025-02135-w. Epub 2025 Feb 14.

Short-term pulse pressure variability: a novel prognostic marker and therapeutic target in patients with vascular Ehlers-Danlos syndrome? Preliminary results from a pilot study

Giacomo Buso [1,2], Roberto Gatta [3], Federica Corvini [1], Nicola Laera [1], Claudia Agabiti-Rosei [1], Anna Paini [1], Giuseppe Bulgari [1], Beatrice Petroboni [1], Fabio Bertacchini [1], Carlo Aggiusti [1], Deborah Stassaldi [1], Sara Capellini [1], Massimo Salvetti [1], Carolina De Ciuceis [1], Marco Ritelli [4], Marina Venturini [5], Marina Colombi [4], Maria Lorenza Muiesan [6]

Affiliations + expand

PMID: 39953236 DOI: 10.1038/s41440-025-02135-w

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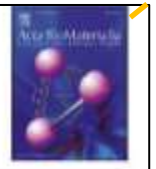
2023



Full length article

Patient-derived extracellular matrix demonstrates role of COL3A1 in blood vessel mechanics

Elizabeth L. Doherty[a,b], Wen Yih Aw[a,b], Emily C. Warren[a], Max Hockenberry[c,d], Chloe P. Whitworth[e], Grace Krohn[a], Stefanie Howell[b], Brian O. Diekman[a], Wesley R. Legant[a,d], Hadi Tavakoli Nia[f], Anthony J. Hickey[b], William J. Polacheck[a,c,g,*]

Fibulina1
Fibulina 4

TGFBeta1
Tenascina X

The prevailing hypothesis has been that the dominant negative effect of COL3A1 variants on collagen III assembly results in compromised mechanical properties of the arterial wall that renders vessels susceptible to rupture. Here, using a novel method for studying ECM generated by patient donor cells, it has been demonstrated that the **effects of COL3A1 mutations on ECM biochemical and biophysical properties depend on genotype**, and that the underlying mechanism that results in aneurysm formation and progression could depend on the specific type of causal mutation. Furthermore, these results suggest that matrix constituents other than type III and type I collagen could provide targets for therapeutic intervention for vEDS. The observation that EC migration is regulated by the mechanical consequences of COL3A1 mutations in the ECM highlights a potential role of endothelial cells in vEDS disease progression and motivates further investigation into the role of the vascular endothelium in disease progression.

empty

full

AVAILABLE RESOURCES

International Guidelines supporting practice (ESC 2024)
Mildly-to-moderately effective drugs (betablockers, sartans)
Healthy Lifestyle to promote (nutritional supplementation, mild exercise)
Patients' Associations
Reference Care Centers

UNMET NEEDS

- Prognostic biomarkers to personalize monitoring
- Therapeutic biomarkers to personalize pharmacological prevention
- Preclinical research focused on patients' priorities
- Multicenter initiatives to maximize patients' enrollment

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