Medical Management and Surveillance in Vascular Ehlers-Danlos Syndrome (vEDS)

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

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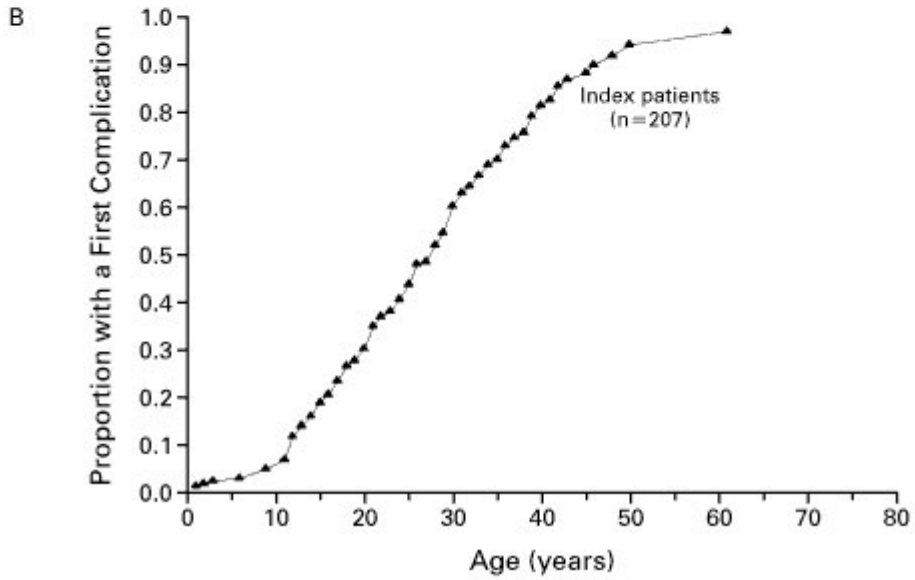
Barnes-Jewish Hospital
BJC HealthCare

Disclosure: Chair, Event Adjudication Committee, DISCOVER trial

vEDS: Natural History and the Need for Effective Therapies

- 2000 Pepin et al. Median survival 48 years with 80% of individuals experiencing complications by age 40 years (1).

- Increased risk of vascular events in men at younger ages (2).



- Improved prognosis reported in more recent “clinical history” studies.

Frank et al. 144 patients followed 2000-2017 (3)
Survival rate of 72% over 5-years and over 80% at age 50 years

Bowen et al. UK Observational study 2023 (4)
Survival rate of 90% over 5-years

[1]Pepin M et al. NEJM 2000;342:673
[2]Pepin M et al. Genet Med 2014;16:883
[3]Frank M et al. JACC 2019;73:1948
[4]Bowen JM et al. J Hum Genet 2023;31:749

Why the Improvement in Prognosis in vEDS?

- Improved recognition (cascade testing), wider availability of genetic testing

- Centers of excellence with dedicated protocols for evaluation and management (imaging, surveillance, education, **pharmacotherapy**, intervention).

Frank study: 90% of patients on celiprolol
Survival better for celiprolol-treated patients compared to no Rx (72% vs 52%).

Bowen study: 5-year survival better for any CV medication (BB/ARB) compared to no Rx (97% vs 43%)

Pharmacotherapy in vEDS: **Celiprolol**

- Third generation beta blocker (BB) with unique properties—”*selective adrenoreceptor modulator”*:
  - β1-antagonist (decrease HR and contractility)
  - β2-partial agonist (vasodilation)
  - β3-agonist (coronary vasorelaxation)
  - Stimulate endothelial nitric oxide synthase (vasodilation)

- Celiprolol reduces systolic and diastolic BP and MAP.
- Less HR reduction compared with some other beta-blockers.
- No documented increased peripheral resistance.

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  - Nitric oxide release (vasodilation)

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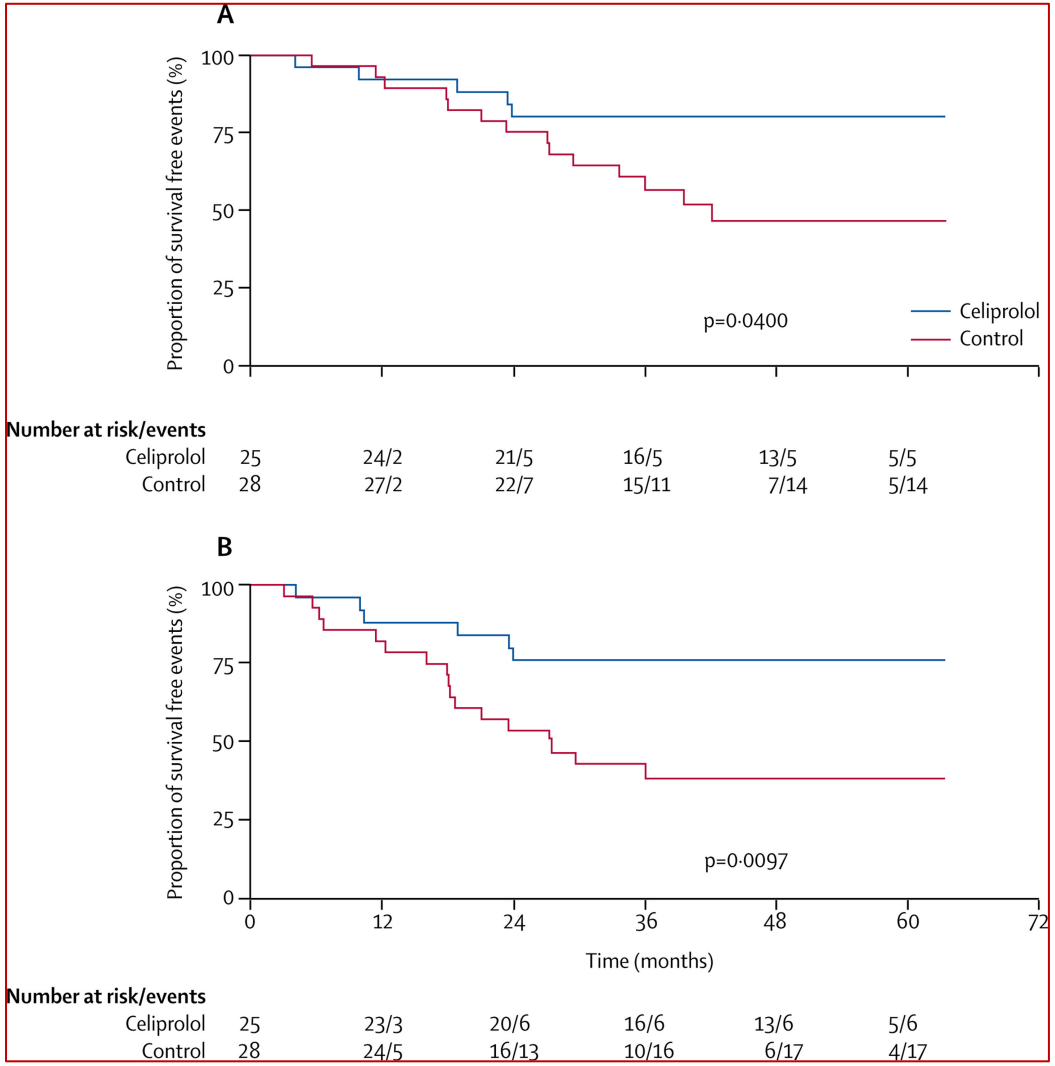
No documented increased peripheral resistance.

"The exact mechanism of the (purported) beneficial effect in vEDS is not fully understood—interaction via TGFβ inhibition or endothelial nitric oxide synthase activation has been postulated." De Backer and De Backer JACC 2019

BBEST Study: Ong et al, Lancet 2010

53 patients with ***clinical dx*** of vEDS (33 with molecular dx) randomized to celiprolol vs. placebo

- Target dose 400 mg/day
- Mean follow-up 47 months
- Trial stopped early for benefit, as celiprolol led to a 3-fold reduction in arterial ruptures or dissection in treatment arm (HR 0.36; 95% CI 0.15-0.88; p = 0.04).

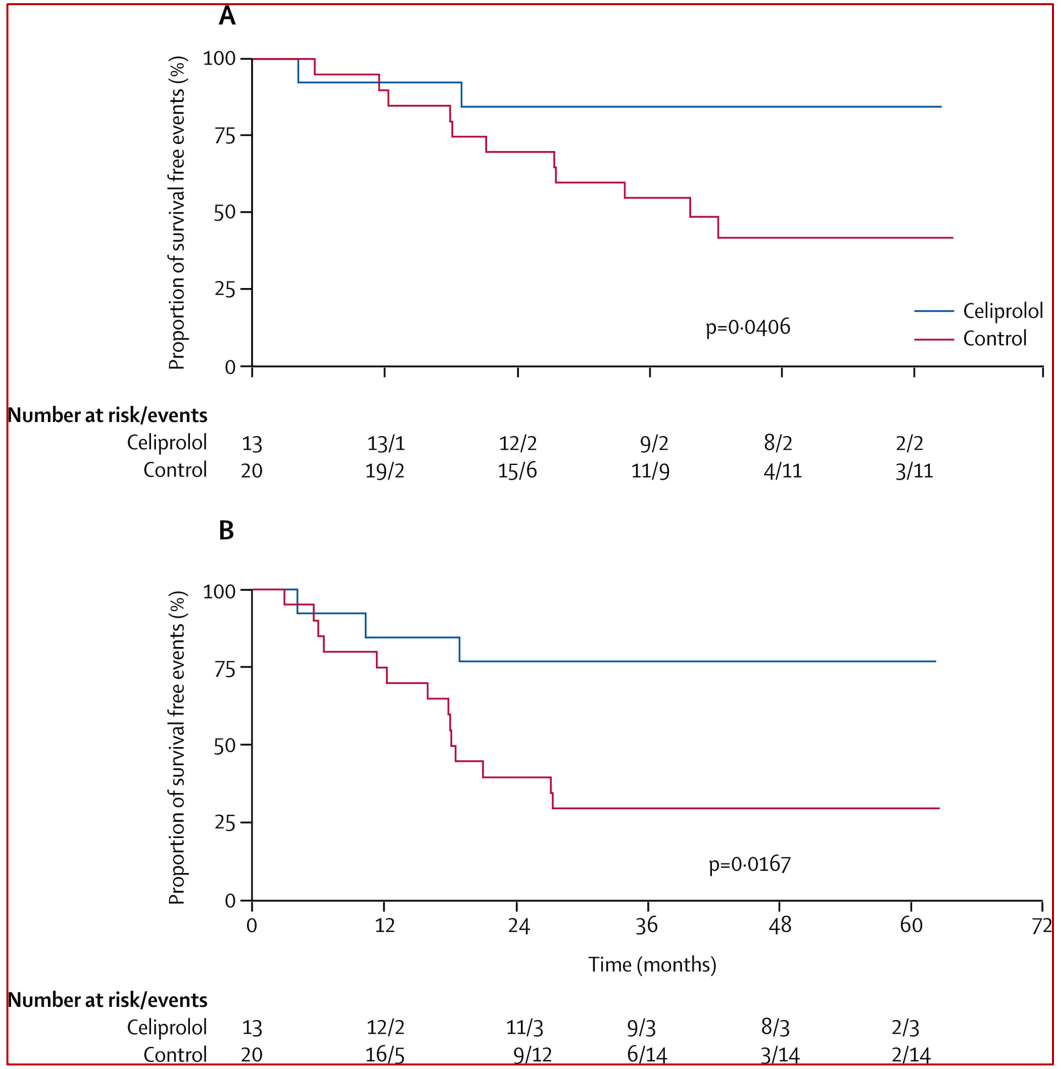


BBEST Study: Ong et al, Lancet 2010

Criticisms of the trial:

- Only 33/53 patients had molecular confirmation with *COL3A1* mutations
- concerns about matching of patients and controls

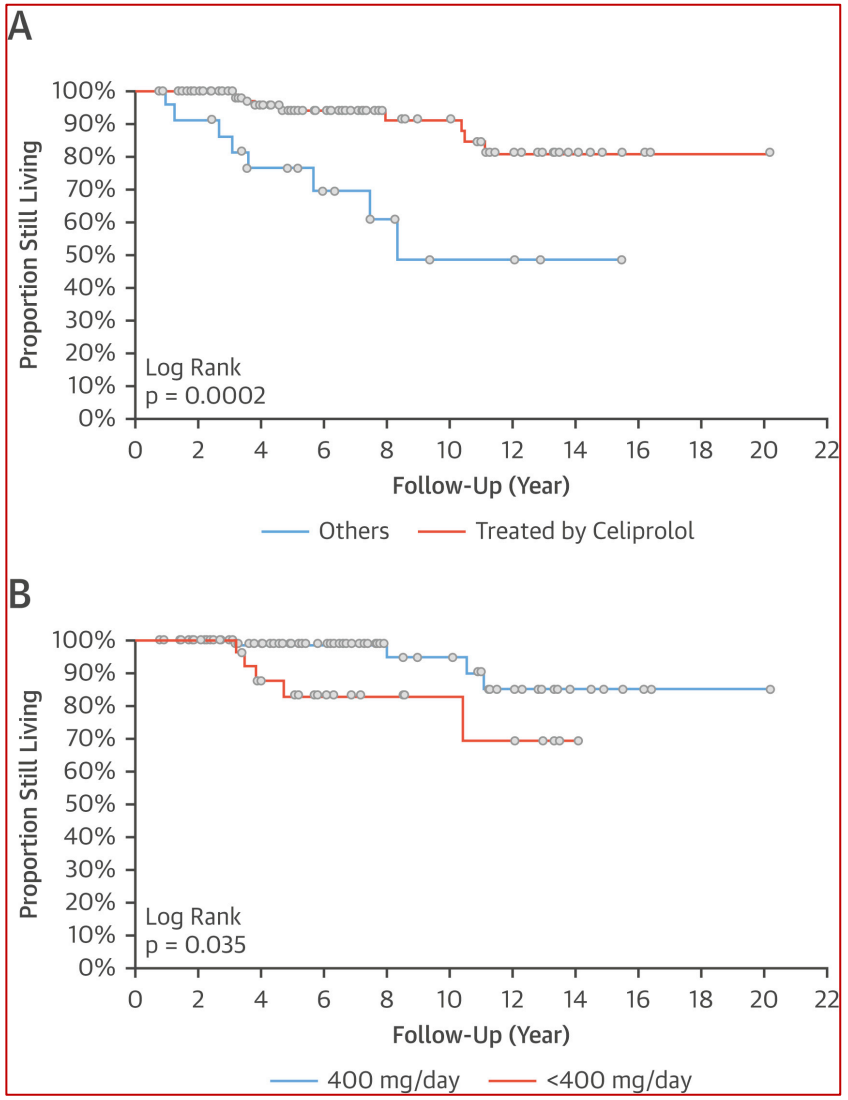
Outcomes of *COL3A1*+ patients:



Kaplan-Meier curves of event-free survival in 33 patients with positive *COL3A1* mutation Primary endpoint (A). Primary and secondary endpoints (B).

2019 Frank Study: JACC 2019;73:1948-57

- Retrospective study of 144 patients with molecular confirmed vEDS (*COL3A1* mutation) 2000-2017 French referral center
- All pts recommended celiprolol with target dose 400 mg/day
- Overall survival 72% at 5-years
- Celiprolol-treated pts had improved survival with dose-dependent effect (better with 400 mg/d)



Other Observational Studies of Pharmacotherapy in vEDS

2021 Baderkhan et al. Eur J Vasc Endovasc Surg 2021;61:326-31

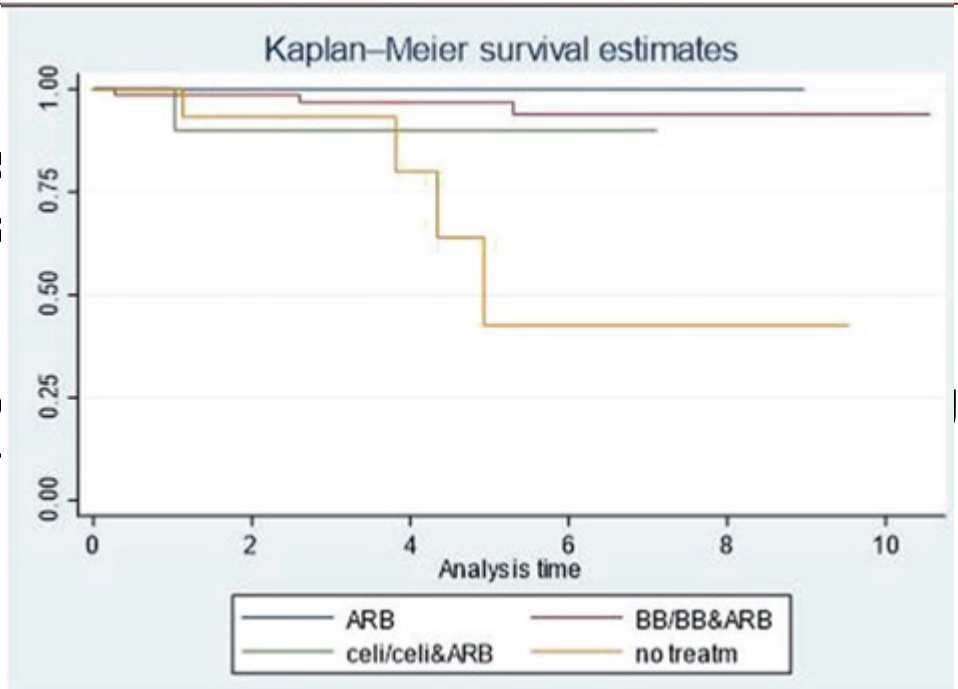
- 40 patients (Sweden) with vEDS offered celiprolol rx, 2011-2019
- 22-month follow-up:
  Celiprolol treated patients: 4.5% annual risk of vascular event

2023 Buso et al. Vasc Med 2023;29:265-73

- 26 patients (Italy) with vEDS all on celiprolol (80% @400 mg/d)
- Yearly risk of vascular event: 9%

Other Pharmacotherapy in vEDS: Role of ARBs

- Angiotensin II infus .
  - Multiple mecha
- Animal studies hav iotensin II antagonism in vascular protectior



- Bowen JM et al (UK). Eur J Hum Genet 2023;31:749-60.
  Retrospective study 126 pts with *COL3A1* vEDS

  Regardless of CV drug used: celiprolol, other BB, and/or ARBs, alone or in combination, had improved outcome compared to untreated patients (97% vs 43%).

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

ARCADE Trial: Angiotensin II Receptor Blockage in Vascular Ehlers-Danlos Syndrome

- multicenter, placebo-controlled RCT to evaluate efficacy of **irbesartan (ARB)** in adults with vEDS on stable background therapy with celiprolol (trial duration 2 yrs)

- **Primary outcome**: composite of fatal or nonfatal arterial events or worsening arterial lesions

- **Secondary outcomes**: each component of primary outcome, # arterial lesions at imaging; time to first symptomatic CV event; symptomatic non-cardiovascular vEDS event.

Jeunemaitre et al. Circulation 2025:151;686-695

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

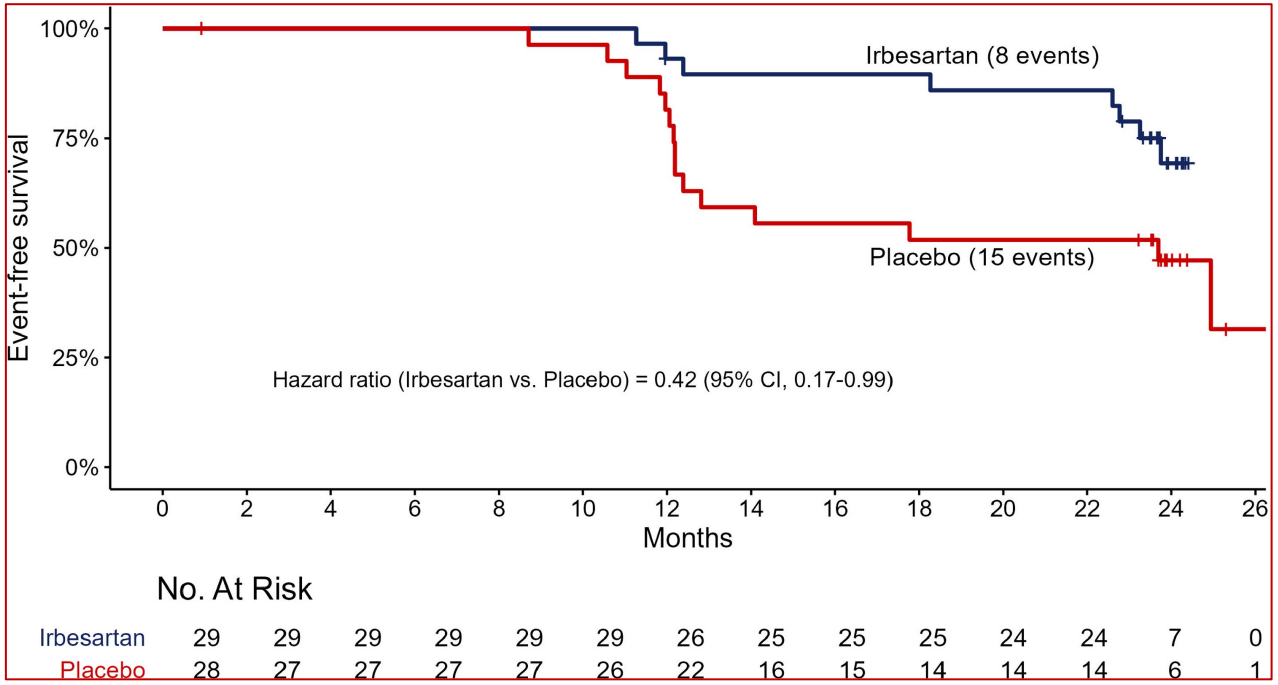
ARCADE Trial 57 pts enrolled

- Symptomatic arterial events reduced by ARB

  28% Irbesartan
  54% placebo
  HR 0.42, CI 0.17-0.99

- Reduction of progression of arterial lesions was seen at all sites.

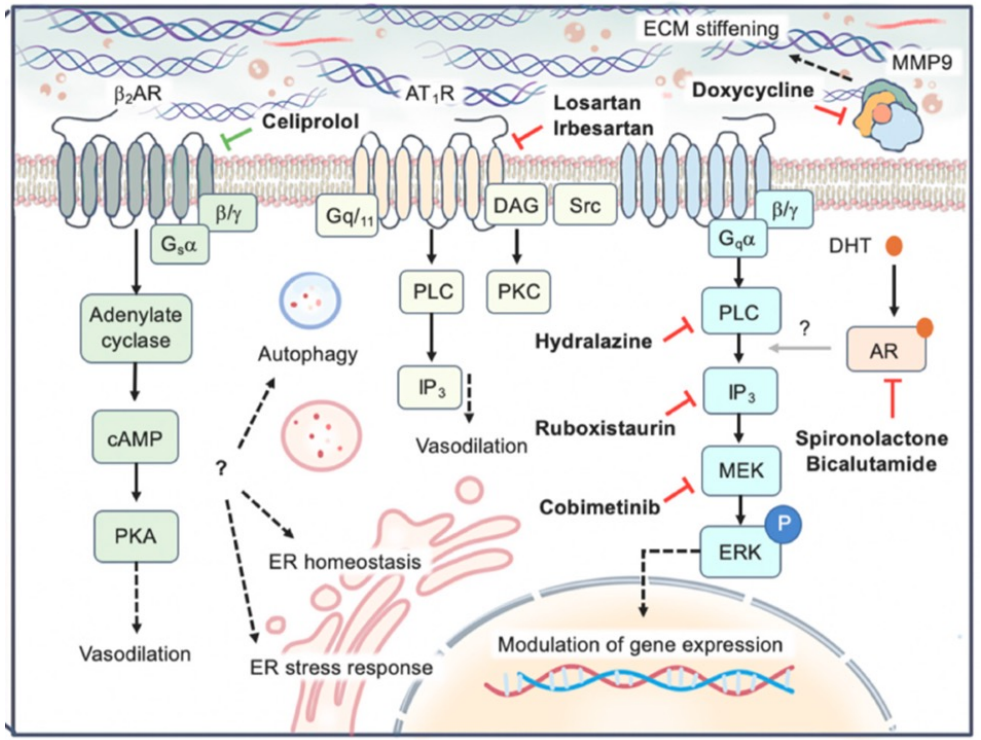
- Irbesartan reduced SBP 5.4 mm



Jeunemaitre et al. Circulation 2025:151;686-695

Experimental Evidence of Targets for Pharmacotherapy in vEDS

- Complex pathways involved in cell growth, differentiation, and survival.
- Multiple potential targets to potentially modulate disease in vEDS.



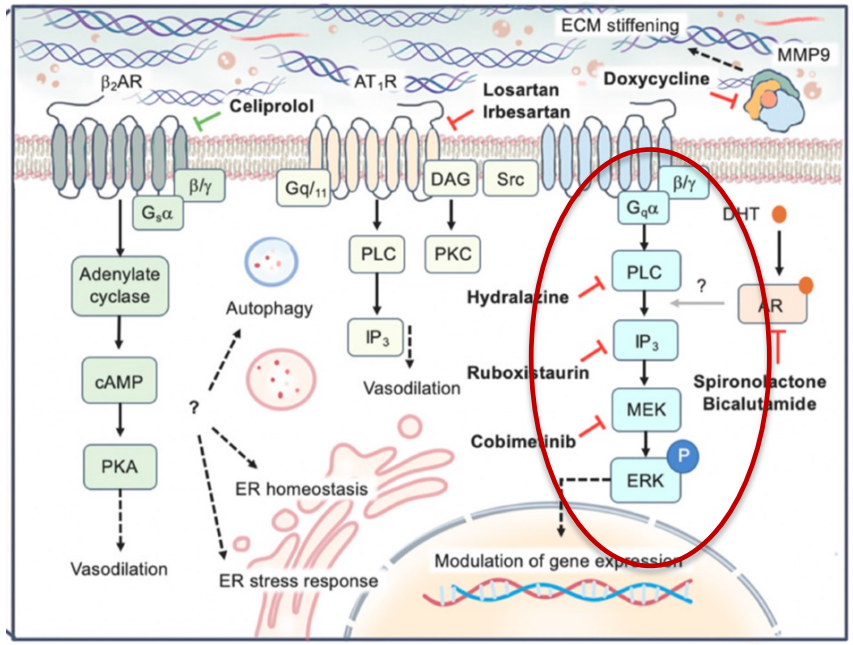
Buso et al. J Clin Med 2024;13:4255

Experimental Targeting of Pathways as Potential Pharmacotherapy in vEDS

Bowen CJ et al (Hopkins). J Clin Invest 2020;130:686-98.

Knock-in COL3A1$^{G209S/+}$ and COL3A1$^{G938D/+}$ mice

- Role of the PLC/IP3/PKC/ERK signaling pathway in vascular disease.



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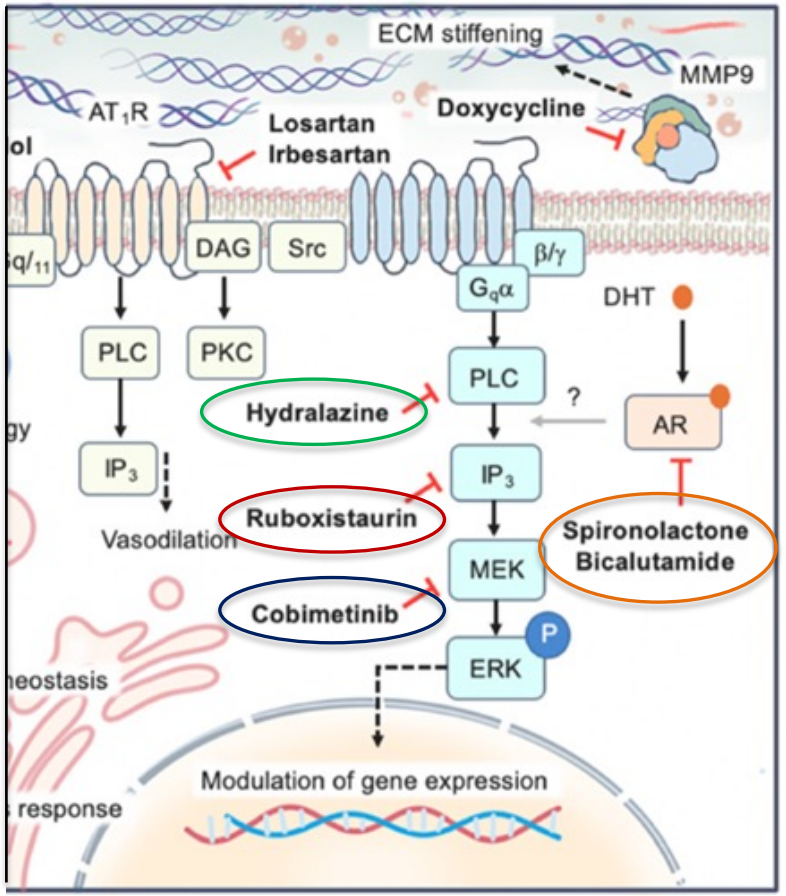
***Ruboxistaurin*—PKCβ inhibitor** [improves endothelial function] improved survival @45 days (94% vs 52%).

***Cobimetinib*—MEK inhibitor** improved survival @45 days to 90%

***Hydralazine*—IP3**-inhibitor blocking ER Ca^{++} release and **PKCβ** activation improved survival---but protection was abruptly lost at time of sexual maturity [esp. in males].

***Bicalutamide*—androgen receptor blocker**—increased survival in both sexes

***Hydralazine plus spironolactone*---**increased survival



Experimental Evidence of Potential Targets for Pharmacotherapy in vEDS

Legrand et al (Paris, FR). PLoS Genet 2022;18, e1010059.

Knock-in COL3A1^{+G182R} mice

Treated with celiprolol, propranolol, amlodipine, losartan, hydralazine.

- The only medication that significantly reduced the risk of aortic rupture was losartan.
- Discontinuation of losartan led to return to increased mortality.

Prevention of Rupture with Enzastaurin in Vascular Ehlers-Danlos Syndrome (PREVEnt) Trial

- Enzastaurin—another PKCβ/P13K/AKT signaling inhibitor [used in brain tumors].
- Multicenter, double-blind, placebo-controlled RCT of Enzastaurin [AR101] 500 mg/day vs placebo to prevent vascular events in vEDS.

October 2022: indefinite suspension of trial due to lack of funds.

DISCOVER trial: Celiprolol vs Placebo in vEDS

Sponsor: Zevra Therapeutics

- >15 years old
- USA
- Genetic confirmation of *COL3A1* LP/P variant
- Baseline MRA
- No arterial rupture or dissection or uterine/intestinal rupture within past 6 months
- Participants may remain on any current non-BB therapy, including ARBs

What is Current Pharmacotherapy in vEDS?

*Beta blocker (?3rd generation BB in USA [nebivolol, carvedilol] or celiprolol elsewhere)

*Irbesartan/ARBs

Considerations:

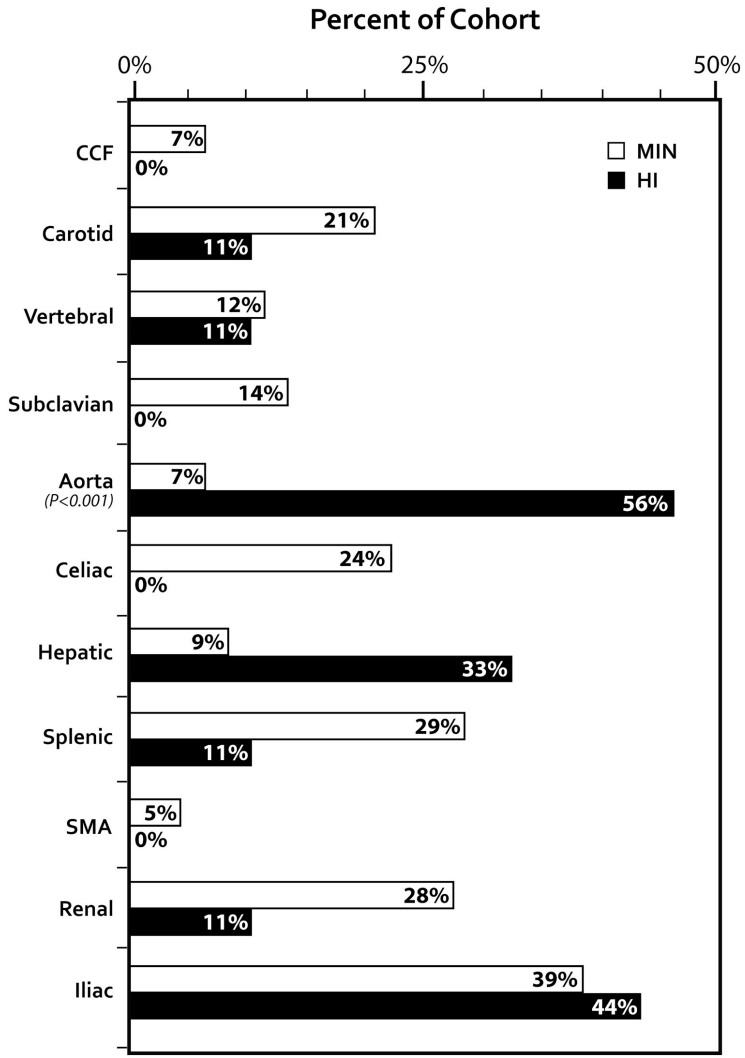
?Spironolactone

?hydralazine (if on BB and if HTN)

Imaging Protocols in vEDS

- In older children and adults, expert consensus opinion is to obtain head to pelvis cross sectional imaging (MRA or CTA) at diagnosis. This has potential to discover preclinical lesions that may become actionable.

- Subsequent imaging occurs at ~2-year intervals unless arterial abnormalities are discovered (such as aneurysm, pseudoaneurysm, or dissection) occur or after acute arterial events.



Shalhub et al. J Vasc Surg 2014

Imaging Protocols in Children with vEDS

- Cross-sectional imaging from head to pelvis should be performed but may be delayed until after age 3 years to avoid risks of sedation.
- Serial imaging is driven by associated risk factors and baseline findings.

Morris SA et al. Circulation 2025

Pharmacotherapy in Vascular Ehlers-Danlos Syndrome (vEDS): Conclusions

- Pharmacotherapy in vEDS includes a **beta-adrenergic blocker** (In USA beta blocker [3rd generation (carvedilol, nebivolol)], elsewhere, celiprolol) and an **ARB** (irbesartan).

- Clinical investigation is needed to understand the potential role of additional pharmacotherapy in vEDS [spironolactone, hydralazine, ruboxistaurin, enzastaurin]

Alan C. Braverman, MD

abraverm@wustl.edu

Thank you!