Medical Treatment Of Patients With Vascular Ehlers Danlos Syndrome: How Does Celiprolol Treatment Work And How Does It Help

Professor Martin Björck, Uppsala, Sweden
Past President of the ESVS
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Conflict of interest:

- Consultant for Acer Therapeutics when designing the DiSCOVER Trial
- Member of the Independent Adjudication Committee of the DiSCOVER Trial
- Acer was acquired by Zevra therapeutics in November 2023

Vascular Ehlers-Danlos Syndrome (vEDS)

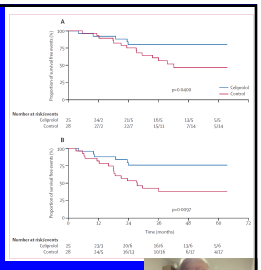
- Autosomal dominant inherited pathogenic sequence variation of the COL3A1
- Estimated > 3 000 patients in the USA
- The most lethal connective tissue disease, a nightmare for the vascular surgeon
- Dissections and ruptures of the aorta and main arteries
- Spontaneous ruptures of hollow organs (oesophagus, colon and uterus)

Celiprolol is not similar to other betablockers

- A cardioselective β_1 blocker with a β_2 agonist vasodilatory effect
- This unique combination of effects reduces the heart rate, mean arterial and pulse pressures
- Decreases mechanical stress on arterial collagen fibres Increased synthesis of collagen was observed in animal experiments (Pleiotropic effect?)

BBEST trial, Lancet 2010

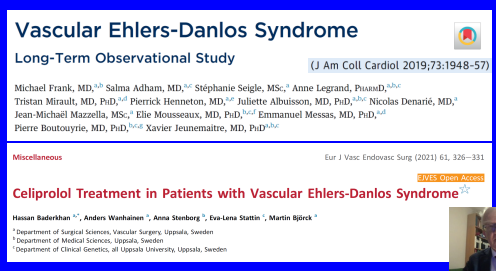
RCT, 25+28 patients
France and Belgium
FU a mean of 4 years
Terminated prematurely
Arterial rupture in 20% and 50%
Hazard ratio of 0.36



The Uppsala experience

- Uppsala is a national referral centre for vEDS patients
- In our cohort the annual event rate is 4.7%, among those treated with celiprolol, similar to the treatment arm in the BBEST trial (5%), lower than in the placebo arm (12%)

Cohort studies from France and Sweden



Vascular Ehlers-Danlos Syndrome

Long-Term Observational Study

(J Am Coll Cardiol 2019;73:1948-57)

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Miscellaneous

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Celiprolol Treatment in Patients with Vascular Ehlers-Danlos Syndrome☆

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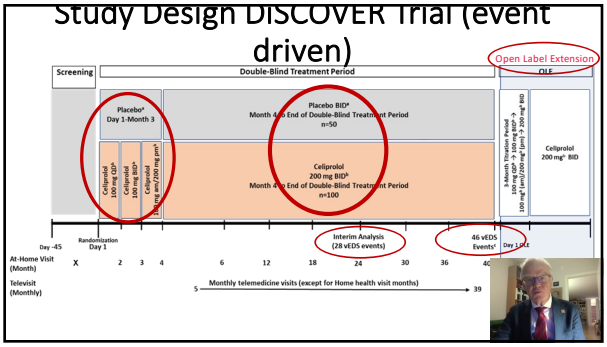
Celiprolol not available for vEDS in the USA

- Despite being used in Europe, where celiprolol was already registered for treatment of hypertension
- The FDA did not accept Acer Therapeutics first application
- They required more evidence, resulting in the design of the DiSCOVER trial
- The start of the trial was delayed by the pandemic
- First patients recruited in December 2022

Study Design DISCOVER Trial (event driven)



Inclusion criteria (n=5)

- Informed Consent
- Magnetic resonance angiogram (MRA) image at baseline
- A genetic test confirming pathogenic COL3A1 variant
- Patients must be ≥ 15 years of age at the time of randomization (an important subgroup 15-18 years)

Inclusion halted in April 2023

- Acer (a small drug company) experienced financial difficulties after the negative results from another trial It was acquired Zevra Therapeutics
- To ensure continuation of the Celiprolol DiSCOVER trial, recruitment was halted in April 2023, when 17 patients had been recruited (of 150)
- Zevra restarted trial enrolment in May 2024 and since then has been actively enrolling patients
-


Take-home message
Celiprolol and vEDS
• Celiprolol adds safety to this very vulnerable patient group
• The DiSCOVER trial will add more robust evidence
• Many US patients travel to Europe for prescription
• Enrolling in the trial is a better option