# Celiprolol Treatment in Patients with Vascular Ehlers-Danlos Syndrome☆

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**WHAT THIS PAPER ADDS**

The French/Belgian Beta blockers in Ehlers-Danlos Syndrome Treatment (BBEST) trial reported in 2010 that the number of serious/fatal vascular events could be halved by treating patients with vascular Ehlers-Danlos syndrome with celiprolol. Prior to that publication, no evidence based treatment could be offered to patients or their relatives carrying the same pathogenic variant of the procollagen 3A1 gene. This disease is rare, explaining why this is the second largest cohort published on celiprolol treatment. Although treatment is well tolerated in most cases, it is important to know more about the side effects, to enable the treatment of the highest number of patients, if possible, with the full dosage (400 mg daily).

**Objective:** Vascular Ehlers-Danlos syndrome (vEDS) is a rare monogenetic disease caused by pathogenic variants in procollagen 3A1. Arterial rupture is the most serious clinical manifestation. A randomised controlled trial, the Beta-Blockers in Ehlers-Danlos Syndrome Treatment (BBEST) trial, reported a significant protective effect of the beta blocker celiprolol. The aim was to study the outcome of celiprolol treatment in a cohort of Swedish patients with vEDS.

**Methods:** Uppsala is a national referral centre for patients with vEDS. They are assessed by vascular surgeons, angiologists, and clinical geneticists. Family history, previous and future clinical events, medication, and side effects are registered. Celiprolol was administered twice daily and titrated up to a maximum dose of 400 mg daily. Logistic regression was used to analyse predictors of vascular events.

**Results:** Forty patients with pathogenic sequence variants in *COL3A1* were offered treatment with celiprolol in the period 2011—2019. The median follow up was 22 months (range 1—98 months); total follow up was 106 patient years. In two patients, uptitration of the dose is ongoing. Of the remaining 38, 26 (65%) patients reached the target dose of 400 mg daily. Dose uptitration was unsuccessful in six patients because of side effects; one died before reaching the maximum dose, and five terminated the treatment. Five major vascular events occurred; four were fatal (ruptured ascending aorta; aortic rupture after type B dissection; ruptured cerebral aneurysm; and ruptured pulmonary artery). One bled from a branch of the internal iliac artery, which was successfully coiled endovascularly. The annual risk of a major vascular event was 4.7% ($n = 5/106$), similar to the treatment arm of the BBEST trial (5%) and lower than in the control arm of the same trial (12%). No significant predictor of vascular events was identified.

**Conclusion:** Treatment with celiprolol is tolerated in most patients with vEDS. Despite fatal vascular events, these observations suggest that celiprolol may have a protective effect in vEDS.

**Keywords:** Celiprolol, *COL3A1*, Drug therapy, Ehlers-Danlos syndrome, Pathogenic sequence variants, Vascular type
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## INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a heterogenous group of genetic connective tissue disorders, characterised by tissue fragility, skin hyperextensibility, and joint hypermobility. Vascular EDS (vEDS) is the most severe type of EDS, associated with fatal ruptures in arteries and other organs rich in type III collagen, such as the oesophagus, colon, and uterus. The pattern of inheritance of vEDS is autosomal dominant and caused by pathogenic sequence variants of *COL3A1*, which codes for procollagen III, resulting in qualitative and quantitative abnormalities of type III collagen.[2] vEDS comprises approximately 5% of all EDS, and the median survival has been estimated to be 48 years. By 20 years of age, 25% of patients with vEDS, and by 40 years of age

☆ Preliminary results on 33 patients were presented at the ESVS 33rd Annual Meeting, September 2019, in Hamburg, Germany.[1]

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80%, have experienced at least one complication.[3,4] The most common cause of death is arterial rupture. The risks to pregnant women with vEDS is approximately 5% for pregnancy related death, which is mostly due to arterial complications.[5] In spite of this, it is not certain that avoiding pregnancy affects survival. With early caesarean section, severe lacerations may be avoided.[6] Clinically, the disease is characterised by the presence of some of the Villefranche diagnostic criteria.[7] The diagnosis needs to be confirmed by molecular genetic analysis of *COL3A1* or a biochemical test of the collagen (through tissue cultures of fibroblasts). Pathophysiologically, patients with vEDS have low intima—media thickness and high mechanical stress on the wall of elastic arteries, and hence an increased risk of arterial dissection and rupture.[8]

Celiprolol is a cardioselective $\beta_1$ blocker with a $\beta_2$ agonist vasodilatory effect, a rather unique combination of effects that reduce the heart rate, and mean and pulse pressure in hypertensive patients.[9] Using celiprolol in vEDS is believed to decrease mechanical stress on collagen fibres within the arterial wall, and thereby reduce their fragility.[10] In recent years there has been more focus on the association between $\beta$ adrenergic stimulation and the expression of transforming growth factor $\beta$ (TGF-$\beta$) as more probable mechanisms of action of celiprolol.[11] Beta blockers have been evaluated previously in patients with Marfan syndrome, with some effect on slowing the rate of aortic dilatation and reducing the risk of aortic complications.[12] A randomised controlled trial (RCT), the Beta-Blocker in Ehlers-Danlos Syndrome Treatment (BBEST) trial was published in 2010, comparing celiprolol treatment to a control placebo group.[10] The trial showed effective prevention of major events in the celiprolol group *vs.* the no treatment group. After a mean follow up of 47 months, the primary endpoint (a composite endpoint of arterial rupture or dissection, fatal or not) was recorded in five (20%) of 25 patients in the celiprolol group *vs.* 14 (50%) of 28 controls (hazard ratio 0.36, 95% confidence interval 0.15—0.88; $p = .040$).

The new European Society for Vascular Surgery clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysm recommend that patients with an aortic disorder suspected of having underlying genetic cause be referred to and managed by a multidisciplinary team at a highly specialised centre.[13] Uppsala is such a unit, with a special interest and national responsibility for patients with vEDS. After the publication of the BBEST trial Swedish patients with vEDS began to be treated with celiprolol. The aim of the present study was to report the feasibility and outcome of celiprolol treatment in this cohort of patients.

## MATERIALS AND METHODS

A multidisciplinary team of vascular surgeons, angiologists, and clinical geneticists takes care of patients with vEDS and other connective tissue diseases at the authors' unit. After verification of the diagnosis by molecular genetic analysis, the patients were offered celiprolol treatment. Celiprolol is not a licensed medication in Sweden and for each patient a special application form was submitted to the Swedish Medical Products Agency (SMPA). Two angiologists continued to have regular contacts with the patients during the course of the treatment. Patients living far away were sometimes treated in collaboration with local physicians. The starting dose of celiprolol was 100 mg, which was to be progressively uptitrated to 400 mg (200 mg twice daily).[10] The uptitration was every 6 months at the beginning of the study period, but was later changed to every three months if the medication was well tolerated.

The American College of Medical Genetics and Genomics guidelines was used to classify sequence variants. Event free survival stratified by mutation type was examined by Kaplan—Meier curves, and the sequence variants categorised in three different groups (group 1: splice site variants; group 2: glycine exchange to a larger bulky amino acid; and group 3: glycine exchange to a smaller residue).[14]

The fact that each patient had a granted application to the SMPA made it easy to identify them. Family history, previous and current clinical events and manifestation, medication, and treatment side effects were collected retrospectively. The study was approved by the (national) Swedish Ethical Review Authority.

### *Statistical analysis*

Data analysis was performed using SPSS Statistics 23 (IBM, Armonk, NY, USA). Data were assessed for normality with histograms. Mean or median and standard deviation or range for continuous variables, and proportions and frequencies for categorical variables were used for statistical analyses. The effect of potential predictors on life threatening events during celiprolol (EC number: 260-752-2) treatment was assessed by univariable logistic regression. All variables (age, end dose of celiprolol, baseline diastolic blood pressure (BP) $<$ 62 mmHg, baseline pulse pressure $>$ 50 mmHg, and pulse pressure after treatment $>$ 50 mmHg) that on unadjusted analysis achieved a $p$ value $<$ .20 were introduced into a multivariable logistic regression model. A $p$ value $<$ .050 was considered to be statistically significant.

## RESULTS

Between 2011 and 2019, 40 patients with vEDS were referred to and treated with celiprolol at the authors' centre. The median length of follow up was 22 months (range 1—98 months). The mean follow up index, measured from the initiation of celiprolol treatment to the last follow up date, divided by the time to 31 December 2019, was 0.83. Patient baseline characteristics are given in Table 1. Most of the patients had either a strong family history of genetically verified vEDS, or a family history of serious events suspected to be secondary to vEDS (i.e., the relative's diagnosis had not been verified by molecular genetic evaluation). For details, see Table 2. Of those 40 patients, 19 were first degree relatives from six different families. All

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patients in this cohort had verified molecular genetic variants in *COL3A1*. There were 20 different sequence variants; in 17 of them the glycine was substituted and in 12 the glycine was substituted with a larger amino acid. There were three splice variants, of which one was of uncertain significance (c.1869+6T>G). The details of all sequence variations are shown in Table S1 (see Supplementary Material). The patient with the variant of uncertain significance had a clinical diagnosis of vEDS, and experienced arterial dissections in six different arteries. Whole body magnetic resonance imaging (MRI) screening was performed in 19 patients and whole body computed tomography in two. The patients were offered whole body MRI imaging at the first evaluation and then every five years thereafter. The patients were told that a positive finding was not always possible to treat, explaining why only about half of the patients were imaged. No new significant findings were observed during those screening examinations.

The investigation for suspected vEDS was initiated because of major vascular events ($n = 13$; 32%), spontaneous colonic perforation ($n = 3$; 7%), or positive family history ($n = 24$; 60%).

### Events and manifestations before treatment

Sixteen patients had one or more vascular manifestations before the start of the celiprolol treatment. Four patients (10%) had arterial aneurysms at the aortic arch, internal mammary, and common iliac and carotid arteries. Eight patients (20%) had 13 arterial dissections: one patient with type B aortic dissection, three with dissections in the carotid arteries, three with dissection in the vertebral arteries, and one had dissections in six arteries (coeliac trunk, renal, superior mesenteric, common iliac, vertebral, and carotid; see Table 3). One patient (2%) had a carotid cavernous fistula and an arteriovenous fistula at the base of the skull, with exophthalmos. Seven patients (17%) had experienced diffuse bleeding either spontaneous, or as a result of minor trauma, including haematoma of the rectus muscle, excessive menstrual bleeding, gastrointestinal bleeding, intra- and retroperitoneal venous bleeding, and bleeding of the pleura, spinal canal, and skeletal muscles.

**Table 1. Baseline characteristics and comorbidities in 40 patients with vascular Ehlers-Danlos syndrome studied for celiprolol treatment**

| Characteristics | Patients ($n = 40$) |
|---|---|
| Female | 24 (60) |
| Age − y* | 43.5 (15–78) |
| Follow up time − mo | 22 (1–98) |
| Current smoker | 1 (2) |
| Hypertension | 11 (27) |
| Diabetes mellitus | 1 (2) |

Data are presented as *n* (%) or median (range).
* Age refers to when celiprolol treatment was initiated.

**Table 2. Family history of 40 patients with vascular Ehlers-Danlos syndrome (vEDS) studied for celiprolol treatment**

| Family history* | Patients ($n = 40$) |
|---|---|
| First degree relatives with vEDS | 26 (65) |
| First degree relatives who died of vEDS related causes | 4 (10) |
| First degree relatives with suspected vEDS | 14 (35) |
| First degree relatives who died of vEDS related causes | 12 (30) |

Data are presented as *n* (%).
* Suspected vEDS is defined as having clinical manifestations and severe clinical events of vEDS but without a molecular genetic diagnosis.

The most common non-vascular events are given in Table 3.

### Treatment with celiprolol and events

At the end of follow up, the end dose of celiprolol was 100 mg in four, 200 mg in five, and 400 mg in 26 patients. Five patients terminated the treatment, four because of side effects and one for alleged economic reasons. Eight patients did not achieve a maximum dose of 400 mg, either because of side effects ($n = 6$) or short follow up time ($n = 2$). One patient died before reaching the maximum dose.

Fourteen patients experienced one or more side effects. Six patients had severe side effects that prevented the target dose from being reached, four terminated the treatment as mentioned above, and four patients continued treatment at target dose, despite side effects. The most common side effects were dizziness ($n = 5$), abnormal

**Table 3. Manifestations and events in patients with vascular Ehlers-Danlos syndrome before the initiation of celiprolol treatment**

| Manifestation/event | Patients ($n = 40$) |
|---|---|
| Aneurysm | 4 (10) |
| Dissection | 8 (20) |
| Spontaneous bleeding | 7 (17) |
| Spontaneous colonic perforation | 5 (12) |
| Labour injuries* | 5 (12) |
| Thin translucent skin | 10 (25) |
| Acrogeria (premature ageing of the skin) | 1 (2) |
| Club foot | 7 (17) |
| Hypermobility of small joints | 16 (40) |
| Lower limb varicosity | 13 (32) |
| Carotid–cavernous arteriovenous fistula | 1 (2) |
| Pneumothorax | 3 (7) |
| Gingival recession | 5 (12) |
| Joint subluxation/dislocation | 2 (5) |

Data are presented as *n* (%).
* Labour injuries were one cervix rupture and four perineal/vaginal lacerations. One colonic perforation occurred during labour.

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tiredness ($n = 4$), headache ($n = 2$), nausea ($n = 2$), tendency to fall ($n = 1$), diplopia ($n = 1$), bradycardia ($n = 1$), arthralgia ($n = 1$), syncope ($n = 1$), paraesthesia of the fingers ($n = 1$), and one patient experienced both anxiety and sexual dysfunction. Most of the side effects were temporary and improved after dose reduction. The five patients who interrupted the treatment suffered from headache, imbalance, and dizziness ($n = 2$), hypotension, and deterioration of asthma.

Some of the patients were treated with other medications, either as a single therapy or in combination: angiotensin converting enzyme inhibitors ($n = 5$); angiotensin II inhibitors ($n = 9$); beta blockers ($n = 3$); calcium channel blockers ($n = 4$); and diuretics ($n = 4$).

The mean pulse rate at the start was 76 ± 5.7 beats/minute (bpm) and 70 ± 8.1 bpm at the end of the study ($p = .14$), among those still on celiprolol. The mean systolic BP fell from 127 ± 14.5 mmHg to 120 ± 13.3 mmHg ($p < .001$). The mean diastolic BP changed from 82 ± 14.2 to 75 ± 11.5 mmHg ($p < .001$), and the mean pulse pressure from 45 ± 10.8 mmHg to 44 ± 14.2 mmHg ($p = .021$).

Two patients had a baseline diastolic BP < 62 mmHg and 18 patients had a baseline pulse pressure (systolic BP minus diastolic BP) > 50 mmHg. Of the five patients with life threatening events, three (60%) had baseline pulse pressure > 50 mmHg *vs.* 15 (42%) patients without a life threatening event ($p = .64$). A patient with colonic perforation who initially abstained from celiprolol had a pulse pressure >50 mmHg before the event. He was later treated with celiprolol.

Five major vascular events occurred during treatment with celiprolol, four were fatal. A 59 year old woman died as a result of cardiac tamponade, secondary to type A aortic dissection. She had only received 100 mg celiprolol daily for two months. She had a high pulse pressure (>50 mmHg), both before and at the end of follow up.

A 73 year old man died as a result of subarachnoid bleeding due to rupture of a cerebral aneurysm. He had received 400 mg celiprolol daily for three years. He had a high pulse pressure (>50 mmHg), both before and at the end of the follow up.

A 44 year old man died as a result of ascending aortic rupture. He had been treated with 400 mg celiprolol daily for five years. He had high baseline pulse pressure, but his pulse pressure was unknown at the end of the follow up.

A 62 year old man died as a result of pulmonary artery rupture. He had been receiving 400 mg celiprolol daily for 4.5 years. He had baseline pulse pressures of 40 mmHg but it was >50 mmHg at the end follow up.

The fifth patient had bleeding from an internal iliac artery branch, which was successfully managed by coiling. He had pulse pressures around 30 mmHg at the beginning of the treatment and at the end of follow up.

The total follow up was 106 patient years, and thus the yearly risk of major vascular events was 4.7% ($n = 5/106$). Survival analyses for all patients and for those 26 patients with the target dose of 400 mg are illustrated in Figs. 1 and 2.

Multiple regression analysis could not identify any predictor of life threatening events in the patients on the treatment, although (higher) age at the time of start of celiprolol treatment was borderline significant in adjusted analysis (odds ratio 1.075, 95% confidence interval 1.000—1.156; $p = .052$).

Two patients with classical EDS (pathogenic variants in *COL5A1*), and one patient with a sequence variant of uncertain significance have also been treated with celiprolol but were not included in this study. All of them had a vascular manifestation before but none after the medication was started.

## DISCUSSION

This study reports an experience of celiprolol treatment in 40 patients with a verified molecular genetic diagnosis of vEDS. Sixty-five per cent of the patients reached the target dose of 400 mg and tolerated the medication well. During a total follow up of 106 patient years, five patients suffered major vascular events, four of which were fatal.

The yearly risk of major vascular events in this cohort (4.7%) was comparable to what was seen in the treatment arm of the French—Belgian BBEST RCT (5%), and was much lower than the risk in the non-treated arm (12%) of the same trial. This result was achieved despite the fact that fewer patients in this cohort (n = 26/40; 65%) reached the target dose than patients in the BBEST trial (n = 22/25; 88%). A recent observational study by Frank *et al.*[15] demonstrated that celiprolol treatment improved survival in patients with vEDS, and that the effect was dose dependent, with best protection seen in patients treated with 400 mg daily.

In the present cohort, all five patients with fatal or life threatening events on treatment had a high pulse pressure (>50 mmHg) either at the beginning of the treatment and/or at the end. In the BBEST RCT, a low baseline diastolic BP (<62 mmHg) and a high pulse pressure (>50 mmHg) were predictors for poor response to celiprolol. A high pulse pressure may be associated with vascular events, and lowering the pulse pressure may be used as a criterion for successful medication in future studies. The present analysis was not able to find any predictor for the life threatening events, but it is probably a type II error because of the small cohort. Despite this low number, the study still presents the second largest cohort of patients with vEDS treated with celiprolol.[10] Merging data from multiple cohorts of patients is necessary to answer many outstanding issues regarding the treatment of this rare disease.

The BBEST trial demonstrated a significant (>50%) reduction in the number of fatal vEDS related events in patients receiving celiprolol treatment. The trial was terminated earlier than planned (after 64 months) because of the highly significant, and clinically important, differences between the two arms. One of criticisms of the BBEST trial was the lack of genotype and biomolecular analysis in a large proportion of the patients (only 33/53 [62%] had a

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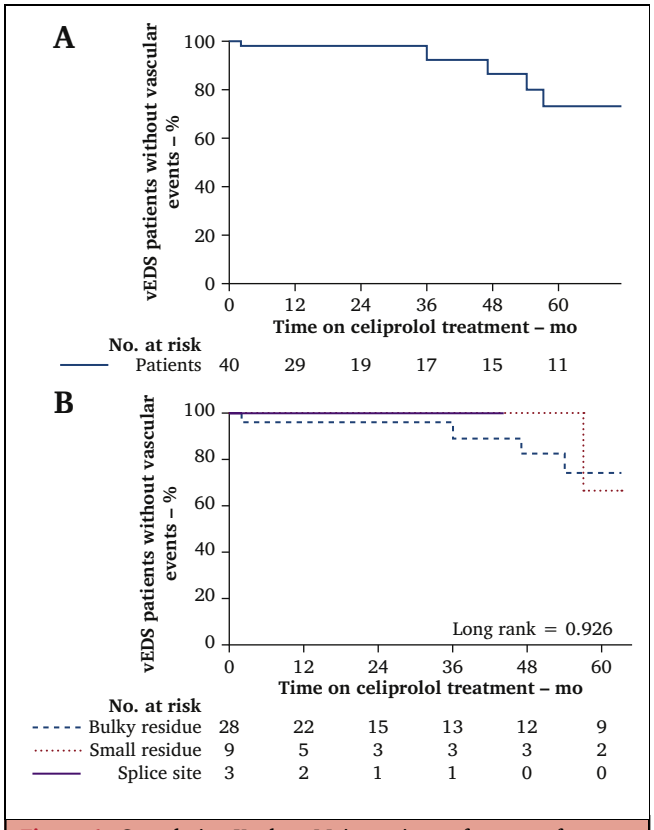


**Figure 1.** Cumulative Kaplan–Meier estimate for event free survival of 40 patients with vascular Ehlers-Danlos syndrome on celiprolol treatment (A) altogether and (B) in genotype groups by the nature of the mutation (see Table S1).

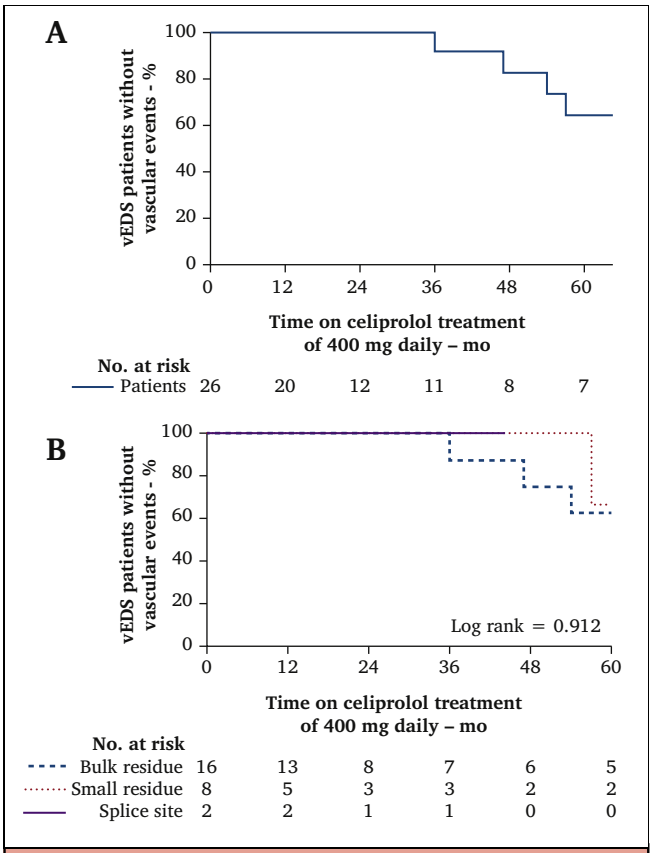


**Figure 2.** Cumulative Kaplan–Meier estimate for event free survival of 26 patients with vascular Ehlers-Danlos syndrome on 400 mg celiprolol daily (A) altogether and (B) in genotype groups by the nature of the mutation (see Table S1).

verified diagnosis), although celiprolol remained effective even after genotype subgroup adjustment. All patients in the present cohort had a molecular genetic diagnosis of vEDS. Three patients who did not have verified pathogenic variants in *COL3A1*, but had clinical manifestations of vEDS, and who were treated with celiprolol, were not included in this report. None of them experienced any vascular events during follow up. Thus, if they had been included, the annual event rate would have fallen.

The mechanism of action of celiprolol in preventing events in patients with vEDS has not yet been clarified. Celiprolol is a $\beta_1$ cardioselective beta blocker with a $\beta_2$ agonist effect. It does not have a BP lowering effect in normotensive patients. In the BBEST trial, as well as in this cohort study, most of the patients were normotensive at the beginning of the treatment. Thus, it is unlikely that the protective effect of celiprolol is mediated through a reduction of BP. However, it is believed that celiprolol provides more stable haemodynamic conditions, and results in less arterial fragility by preventing excessive BP and heart rate peaks during strain and exercise.[16] In addition, celiprolol exerts a $\beta_3$ adrenoceptor agonistic activity in the vascular bed through the endothelium and nitric oxide dependent pathways.[17,18]

A study by Dubacher *et al.* demonstrated that celiprolol improves biomechanical integrity in the aortic wall in mouse models of vEDS.[19] TGF-$\beta$ is necessary for wound healing and collagen synthesis,[20,21] and it has been suggested that $\beta_2$ stimulation by celiprolol enhances collagen synthesis via the TGF-$\beta$ pathway.[11,22]

Peripheral pulse pressure may indicate arterial stiffness, but not reliably.[23] However, increased central pulse pressure is a better indication,[24] and seems to be correlated with disease progression in patients with connective tissue syndromes.[25] Therefore, the plan is to study this further by measuring central pulse pressure in patients with vEDS in an already initiated prospective study.

The main limitations of this study were the low number of included patients and limited follow up. A strength, compared with other cohort studies and the RCT, is that all included patients had a molecular genetic verification of vEDS, and that they were recruited from an ethnically different population.

## Conclusion

Treatment with celiprolol is well tolerated in most patients with vEDS. Despite fatal vascular events, these observations suggest that celiprolol has a protective effect in patients with vEDS. The number of patients in the cohort, and the length of follow up is increasing. Thus, more definite results will be reported in the near future. Furthermore, collaboration with other centres to increase the number of patients is underway.

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## CONFLICTS OF INTEREST

None.

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None.

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Dr Anders Hägg was an important team member in treating these patients with celiprolol. He was also a co-author of the first manuscript submitted, but he died suddenly on June 3rd 2020. As he was unable to participate in the revision of the manuscript, and could not fulfil two of the four ICMJE criteria, he is not included as an author of this paper. However, his contributions were great and decisive, and he is very much missed.

## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2020.10.020.

## REFERENCES

1 Baderkhan H, Stenborg A, Hägg A, Wanhainen A, Björck M. Celiprolol treatment of patients with vascular Ehlers-Danlos syndrome. *Eur J Vasc Endovasc Surg* 2019;**58**. eSupplement 3:e627.
2 Watanabe A, Shimada T. Vascular type of Ehlers-Danlos syndrome. *J Nippon Med Sch* 2008;**75**:254–61.
3 Oderich GS, Panneton JM, Bower TC, Lindor NM, Cherry KJ, Noel AA, et al. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. *J Vasc Surg* 2005;**42**:98–106.
4 Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000;**342**:673–80.
5 Bjorck M, Pigg M, Kragsterman B, Bergqvist D. Fatal bleeding following delivery: a manifestation of the vascular type of Ehlers-Danlos' syndrome. *Gynecol Obstet Invest* 2007;**63**:173–5.
6 Murray ML, Pepin M, Peterson S, Byers PH. Pregnancy-related deaths and complications in women with vascular Ehlers-Danlos syndrome. *Genet Med* 2014;**16**:874–80.
7 Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-danlos national foundation (USA) and ehlers-danlos support group (UK). *Am J Med Genet* 1998;**77**:31–7.
8 Boutouyrie P, Germain DP, Fiessinger J-N, Laloux B, Perdu J, Laurent S. Increased carotid wall stress in vascular Ehlers-Danlos syndrome. *Circulation* 2004;**109**:1530–5.
9 Boutouyrie P, Bussy C, Hayoz D, Hengstler J, Dartois N, Laloux B, et al. Local pulse pressure and regression of arterial wall hypertrophy during long-term antihypertensive treatment. *Circulation* 2000;**101**:2601–6.
10 Ong K-T, Perdu J, De Backer J, Bozec E, Collignon P, Emmerich J, et al. Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial. *Lancet* 2010;**376**:1476–84.
11 Akutsu S, Shimada A, Yamane A. Transforming growth factor betas are upregulated in the rat masseter muscle hypertrophied by clenbuterol, a beta2 adrenergic agonist. *Br J Pharmacol* 2006;**147**:412–21.
12 Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long-term beta-adrenergic blockade in Marfan's syndrome. *N Engl J Med* 1994;**330**:1335–41.
13 Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. Editor's choice – European Society for Vascular Surgery (ESVS) 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms. *Eur J Vasc Endovasc Surg* 2019;**57**:8–93.
14 Byers PH, Belmont J, Black J, De Backer J, Frank M, Jeunemaitre X, et al. Diagnosis, natural history, and management in vascular Ehlers-Danlos syndrome. *Am J Med Genet C Semin Med Genet* 2017;**175**:40–7.
15 Frank M, Adham S, Seigle S, Legrand A, Mirault T, Henneton P, et al. Vascular Ehlers-Danlos syndrome: long-term observational study. *J Am Coll Cardiol* 2019;**73**:1948–57.
16 Caruso FS, Berger BM, Darragh A, Weng T, Vukovich R. Effect of celiprolol, a new beta 1-alpha 2 blocker, on the cardiovascular response to exercise. *J Clin Pharmacol* 1986;**26**:32–8.
17 Abdelkrim MA, Martignat L, Gogny M, Desfontis J-C, Noireaud J, Mallem MY. Celiprolol induces $\beta$(3)-adrenoceptors-dependent relaxation in isolated porcine coronary arteries. *Can J Physiol Pharmacol* 2013;**91**:791–6.
18 De Backer J, De Backer T. Vascular Ehlers-Danlos syndrome management: the Paris way, a step forward on a long road. *J Am Coll Cardiol* 2019;**73**:1958–60.
19 Dubacher N, Munger J, Gorosabel MC, Crabb J, Ksiazek AA, Caspar SM, et al. Celiprolol but not losartan improves the biomechanical integrity of the aorta in a mouse model of vascular Ehlers-Danlos syndrome. *Cardiovasc Res* 2020;**116**:457–65.
20 Wang Y, Ait-Oufella H, Herbin O, Bonnin P, Ramkhelawon B, Taleb S, et al. TGF-beta activity protects against inflammatory aortic aneurysm progression and complications in angiotensin II-infused mice. *J Clin Invest* 2010;**120**:422–32.
21 Dietz HC. TGF-beta in the pathogenesis and prevention of disease: a matter of aneurysmic proportions. *J Clin Invest* 2010;**120**:403–7.
22 Rosenkranz S, Flesch M, Amann K, Haeuseler C, Kilter H, Seeland U, et al. Alterations of beta-adrenergic signaling and cardiac hypertrophy in transgenic mice overexpressing TGF-beta(1). *Am J Physiol Heart Circ Physiol* 2002;**283**:H1253–62.
23 Schillaci G, Pucci G. Aging and pulse pressure widening: the inseparable duo? *J Hypertens* 2015;**33**:2389–91.
24 Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension* 2007;**50**:197–203.
25 Mortensen K, Baulmann J, Rybczynski M, Sheikhzadeh S, Aydin MA, Treede H, et al. Augmentation index and the evolution of aortic disease in marfan-like syndromes. *Am J Hypertens* 2010;**23**:716–24.