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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]

ABSTRACT

BACKGROUND Vascular Ehlers-Danlos syndrome (vEDS) is a rare genetic connective tissue disorder secondary to pathogenic variants within the *COL3A1* gene, resulting in exceptional arterial and organ fragility and premature death. The only published clinical trial to date demonstrated the benefit of celiprolol on arterial morbimortality.

OBJECTIVES The authors herein describe the outcomes of a large cohort of vEDS patients followed ≤17 years in a single national referral center.

METHODS All patients with molecularly confirmed vEDS were included in a retrospective cohort study. After an initial work-up, patients were treated or recommended for treatment with celiprolol (≤400 mg/day) in addition to usual care and scheduled for yearly follow-up. vEDS-related events and deaths were collected and recorded for each patient.

RESULTS Between 2000 and 2017, 144 patients (median age at diagnosis 34.5 years, 91 probands) were included in this study. After a median follow-up of 5.3 years, overall patient survival was high (71.6%; 95% confidence interval: 50% to 90%) and dependent on the type of *COL3A1* variant, age at diagnosis, and medical treatment. At the end of the study period, almost all patients (90.3%) were treated with celiprolol alone or in combination. More than two-thirds of patients remained clinically silent, despite a large number (51%) with previous arterial events or arterial lesions at molecular diagnosis. Patients treated with celiprolol had a better survival than others ($p = 0.0004$). The observed reduction in mortality was dose-dependent: the best protection was observed at the dose of 400 mg/day versus <400 mg/day ($p = 0.003$). During the period surveyed, the authors observed a statistically significant difference in the ratio of hospitalizations for acute arterial events/hospitalizations for regular follow-up before and after 2011.

CONCLUSIONS In this long-term survey, vEDS patients exhibited a low annual occurrence of arterial complications and a high survival rate, on which the overall medical care seems to have a positive influence.
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From the [a]AP-HP, Hôpital Européen Georges Pompidou, Département de Génétique, Centre de Référence des Maladies Vasculaires Rares, Paris, France; [b]INSERM, U 970, Paris Centre de Recherche Cardiovasculaire-PARCC, Paris, France; [c]Université Paris Sorbonne Cité, Faculté de Médecine Paris Descartes, Paris, France; [d]AP-HP, Hôpital Européen Georges Pompidou, Service de Médecine Vasculaire, Paris, France; [e]Service de Médecine Vasculaire, CHU Montpellier, Montpellier, France; [f]AP-HP, Hôpital Européen Georges Pompidou, Service de Radiologie Cardiovasculaire, Paris, France; and the [g]AP-HP, Hôpital Européen Georges Pompidou, Département de Pharmacologie, Paris, France. The French Reference Centre for Rare Vascular Diseases is supported by the French Ministry of Health. The study was also supported by grants from Fondation pour la Recherche Médicale, the Association Française pour les Syndromes d'Ehlers-Danlos, and ANR Grant (NONAGES). This cohort is now part of a national French prospective cohort (RaDiCo SEDVasc), set up by the Rare Disease Cohorts (RaDiCo) INSERM programme funded by the Plan d'Investissements d'Avenir through the Agence Nationale pour la Recherche (ANR-lO-COHO-03-01). The statistical analysis was supported by an agreement between Acer Therapeutics and Assistance Publique-Hôpitaux de Paris. The grantor, however, had no access or influence on the original database, its analysis, or the presentation of findings. Dr. Boutouyrie has provided scientific advice for ACER therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Vascular Ehlers-Danlos syndrome (vEDS) is caused by mutations in collagen, type III, alpha-1 (COL3A1) that usually result in structural changes in the proα1(III) chains encoded by the mutant allele and, rarely, in loss of expression from the allele (1,2). The most common *COL3A1* pathogenic variants are missense substitutions for glycine in the repeating $(Gly\text{-}X\text{-}Y)_n$ sequence of the collagen triple helix, and splice-site variants that lead to in-phase exon skipping (3–5). Both are responsible for a disruption in the assembly of type III homotrimeric collagen fibrils, which causes a dominant negative effect (6). As a result, the production of mature type III collagen is dramatically reduced, which in turn is responsible for an important loss of mechanical strength of arteries and other hollow organs, especially the bowel and uterus (5,6).

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vEDS is considered one of the most severe forms of Ehlers-Danlos syndrome because of its clinical life-threatening complications (6). Acute organ complications start to occur during early adulthood and repeat at unpredictable time intervals (4,7). Spontaneous arterial dissections, aneurysms, and/or ruptures are the most common complications, followed by gastrointestinal perforations (4,6). During pregnancy, and more particularly during the peripartum period, women with vEDS are at an increased risk of arterial and uterine rupture. Median life expectancy has been estimated at 51 years (4,8,9).

Despite progress in our awareness and understanding of the acute complications of vEDS over the past 10 years, there are few options for managing the disease (8,10). Effective prevention of arterial morbidity and mortality by medical treatment has been evidenced in only 1 clinical trial in 2010, BBEST (Beta Blocker in Ehlers-Danlos Syndrome Trial) (11). In this trial, administration of celiprolol, a β1-adrenoceptor antagonist with a β2-adrenoceptor agonist action, resulted in a significant reduction of cardiovascular morbidity and mortality in treated patients. However, limitations of the study included the open-label design, the absence of a placebo arm, and lack of mandatory genetic testing at baseline. Thus, further characterization of the effectiveness of celiprolol for delaying or preventing major arterial events, as well as the practicality of this therapy in daily use over several years in patients with molecularly proven vEDS, are necessary. To address these unmet needs, we report here the results of a long-term follow-up of a large, *COL3A1* pathogenic variant-confirmed vEDS patient cohort.

METHODS

PATIENTS. All patients with clinically and molecularly diagnosed vEDS who were actively followed in the French National Referral Center for Rare Vascular Diseases (Hôpital Européen Georges Pompidou, AP-HP, Paris, France) between January 2000 and March 2017 were screened for participation. During the initial evaluation of the first affected family member seeking medical attention for symptoms related to vEDS (index case), familial medical history was recorded, and an investigation was performed in the first-degree relatives whenever possible. A dedicated database for vEDS was created at our institution in 2011. All relevant clinical data were entered into this database retrospectively from the year 2000 until 2011, and prospectively thereafter until March 15, 2017. The database contains all available medical history related to vEDS before the genetic diagnosis and initial work-up and obtained during the follow-up, either through routine visits or those caused by a new clinical event. Thus, the occurrence of any vEDS-related event was systematically recorded. In case of death during follow-up, the time and cause of death were entered into the database. This study was formally approved by the Ile de France (IDF) ethics committee (IRB registration #00001072), and the database was conducted in compliance with French legislation on patient privacy. The study design and its reporting are compliant with the RECORD statement (12).

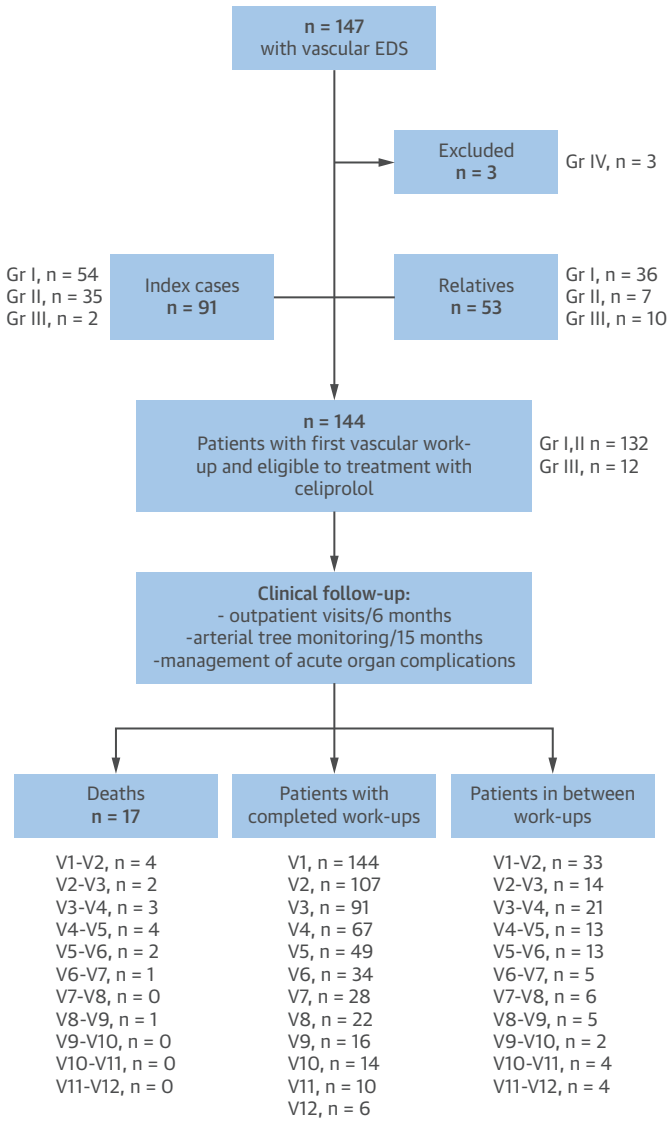
STUDY DESIGN. All vEDS patients were studied by standardized whole-body arterial monitoring by Doppler ultrasound, cardiac computed tomography angiogram, and/or magnetic resonance angiography. Such investigations were performed at baseline (initial assessment at molecular diagnosis) and were repeated every 12 to 18 months in asymptomatic patients. For symptomatic arterial events that occurred before molecular diagnosis, the location of arterial segments was retrieved from hospitalization and imaging reports or examinations, when available. In case of an acute arterial event, symptomatic arterial beds/segments were monitored by any necessary diagnostic and therapeutic means. Between surveillance work-ups, patients were seen for outpatient visits every 6 to 9 months except during celiprolol dose up-titration. To assess arterial morbidity over a long duration in patients with varying follow-up periods, an empirical arterial score was designed for each subject (Online Table 1). The arterial progression score was calculated for each patient at the time of the initial work-up, thus quantifying the history of

ABBREVIATIONS AND ACRONYMS

COL3A1 = collagen, type III, alpha-1

vEDS = vascular Ehlers-Danlos syndrome

FIGURE 1 Patient Flowchart



A total of 144 vascular Ehlers-Danlos syndrome (vEDS) patients were eligible for the study. A majority had glycine missense pathogenic variants (n = 90, Group [Gr] I), others had splice-site variants (n = 42, Gr II), and a third group had variants leading to haplo-insufficiency (n = 12, Gr III).

symptomatic arterial incidents at baseline. Clinical arterial events occurring thereafter were added to the initial score. Patients were divided into 4 levels of clinical progression according to their initial score: very low (score 0 to 1 point), low (score 2 to 8 points), medium (score 9 to 19 points), or high (score ≥20 points). For optimized management of emergencies, patients were given direct access to the medical team at our center.

ADMINISTRATION OF MEDICATION. Since the publication of the BBEST trial, all patients with a positive genetic test at the *COL3A1* gene were offered treatment with celiprolol. Patients taking a beta-blocker were offered celiprolol as an alternative, but this change was not mandatory. Initial dosing of celiprolol was 100 mg once daily and increased by 100 mg/day every month over a 3-month period to reach a maximum dose of 400 mg/day (200 mg twice daily). In case of signs of intolerance (fatigue) during up-titration or follow-up, the dose of celiprolol was reduced by 100 mg/day until the highest tolerated dose was reached. Dose adjustments were made whenever necessary throughout the patient's follow-up if intolerance was suspected. In accordance with the treatment protocol of the BBEST trial, patients were up-titrated to a maximum dose of 400 mg/day. Of 144 patients included in this study, 26 (18%) had previously been enrolled in the BBEST trial.

Adherence to celiprolol was verified by open interview of the patients at each follow-up visit. Patients were considered nonadherent when they disclosed at any time during follow-up that they did not take celiprolol regularly or if they refused treatment. At the occurrence of an acute arterial event and unless contraindicated, patients who were not treated or treated with another drug were once again offered celiprolol as an alternative to their current treatment regimens. To reach significant numbers for a suitable comparative analysis, intolerant patients, patients not taking celiprolol, patients taking another beta-blocker, and nonadherent patients were merged into 1 group further referred to as "not treated."

GENETICS. After initial referral and clinical assessment, patients underwent molecular testing for a *COL3A1* variant after written informed consent. The modalities of molecular analysis have been reported in detail previously (3). After identification of a pathogenic variant, patients were categorized by type of variant: glycine substitution within the triple helix (Group I); splice-site variants, in-frame insertions, deletions, and duplications (Group II); and variants leading to haplo-insufficiency (Group III). Patients with variants of unknown significance were not included in this study.

STATISTICAL ANALYSIS. Quantitative data were expressed as number, median, and first and third quartiles; qualitative data were expressed as number and percentage. Qualitative parameters were compared with the chi-square test or Fisher exact test as appropriate. Quantitative variables were compared with the Wilcoxon Mann-Whitney *U* test or

TABLE 1 Baseline Characteristics of 144 Patients With vEDS According to Treatment

	All Patients (N = 144)	Celiprolol Alone (n = 104)	Celiprolol + Another Drug (n = 26)	Other Drugs (n = 8)	No Treatment (n = 6)	p Value
Sex						0.4201*
Female	87 (60.4)	66 (63.5)	12 (46.2)	5 (62.5)	4 (66.7)	
Male	57 (39.6)	38 (36.5)	14 (53.8)	3 (37.5)	2 (33.3)	
Age at molecular diagnosis	34.5 (25.0–42.5)	32.5 (24.0–40.5)	38.0 (33.0–45.0)	55.5 (41.0–67.5)	31.0 (15.0–51.0)	0.0005
Status						0.0632*
Index case	91 (63.2)	67 (64.4)	19 (73.1)	4 (50.0)	1 (16.7)	
Relative	53 (36.8)	37 (35.6)	7 (26.9)	4 (50.0)	5 (83.3)	
Type of variant						0.0491*
Group I†	90 (62.5)	58 (55.8)	22 (84.6)	5 (62.5)	5 (83.3)	
Group II‡	42 (29.2)	36 (34.6)	4 (15.4)	1 (12.5)	1 (16.7)	
Group III§	12 (8.3)	10 (9.6)	0	2 (25.0)	0	
Baseline characteristics						
BMI, kg/m^2	21.2 (19.0–23.7)	21.0 (19.0–23.0)	22.9 (20.5–26.1)	22.6 (17.3–28.4)	20.6 (19.0–22.5)	0.2415
SBP, mm Hg	114.0 (106.0–123.0)	113.0 (105.0–121.0)	120.0 (112.0–126.0)	112.5 (107.0–131.0)	113.5 (104.0–120.0)	0.2145
DBP, mm Hg	70.0 (65.0–78.0)	70.0 (64.0–76.0)	74.0 (65.0–83.0)	75.0 (68.0–85.0)	69.0 (68.0–76.0)	0.2837
Heart rate, beats/min	72.0 (64.0–81.5)	73.0 (65.0–83.0)	71.0 (65.0–79.0)	64.5 (57.5–69.0)	65.5 (59.0–76.0)	0.0920
Medical history (patients with ≥1 event)						
Overall						0.1319*
Patients	98 (68.1)	69 (66.3)	21 (80.8)	6 (75.0)	2 (33.3)	
Number of events	227	162	47	14	4	
Arterial events						0.0752*
Patients	74 (51.4)	50 (48.1)	19 (73.1)	3 (37.5)	2 (33.3)	
Number of events	156	105	39	9	3	
Gastrointestinal events						0.1603*
Patients	33 (22.9)	27 (26.0)	3 (11.5)	3 (37.5)	0	
Number of events	47	39	4	4	0	
Pulmonary events						0.7937*
Patients	15 (10.4)	11 (10.6)	2 (7.7)	1 (12.5)	1 (16.7)	
Number of events	24	18	4	1	1	
Duration of follow-up, yrs	5.3 (3.2–8.5)	5.1 (3.1–8.4)	7.2 (4.9–11.3)	3.5 (2.9–6.1)	4.3 (1.3–5.2)	0.0123

Values are n (%) or median (interquartile range) unless otherwise indicated. *Fisher exact test for qualitative variables and Kruskal-Wallis test for quantitative variables. †Group I: glycine missense variants. ‡Group II: splice-site variants, insertions-deletions, duplications. §Group III: variants leading to haploinsufficiency.

BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure.

the Kruskal-Wallis tests, as appropriate. Associations between treatment and survival or time until event were examined using the Kaplan-Meier curve. Log-rank test was used to assess the significance. Data were censored if a patient was still alive (or without event) at the end of data collection (March 15, 2017). All tests were 2-sided, and significance was assumed at $p < 0.05$. Statistical analysis was performed with SAS software version 9.2 (SAS Institute, Cary, North Carolina) and XLSTAT software version 2016.4 (Addinsoft, New York, New York).

RESULTS

PATIENT CHARACTERISTICS. Between January 2000 and March 2017, 144 patients with molecularly confirmed vEDS were eligible for participation in this study (Figure 1). A majority had glycine missense variants (n = 90; Group I), others had splice-site variants (n = 42; Group II), and a third group had variants leading to haplo-insufficiency (n = 12; Group III). Patients were followed for a median duration of 5.3 years (interquartile range [IQR]: 3.2 to 8.4 years), the longest documented follow-up being 20 years. Patient baseline characteristics according to treatment are reported in Table 1. As expected, patients were young (median 34.5 years at diagnosis) and had low-normal body mass index (median 21.2 kg/m^2), and blood pressure values (median 114/70 mm Hg), with a slight female predominance. Almost two-thirds of the patients were index cases typically referred for diagnostic work-up due to unusual vascular fragility. Overall, many patients (n = 98; 68.1%) had experienced a disease-related event before follow-up. More than one-half (51.4%) had an arterial event as the first disease-related complication, whereas an inaugural gastrointestinal rupture had occurred in 22.9% of cases (Table 1). There was no difference in the initial

TABLE 2 Clinical Outcomes and Measures in 144 Patients With vEDS at the End of Follow-Up

	All Patients (N = 144)	Celiprolol Alone (n = 104)	Celiprolol + Another Drug (n = 26)	Other Drugs (n = 8)	No Treatment (n = 6)	p Value
Symptomatic events* (patients with ≥1 event)						
Overall						
Patients	53 (36.8)	37 (35.6)	13 (50.0)	1 (12.5)	2 (33.3)	0.2695†
Events	117	75	39	1	2	
Events per 5 yrs	1.6 (0.9–3.0)	1.6 (0.9–2.9)	1.57 (1.1–2.0)	0.9 (0.9–0.9)	44.7‡ (6.4–83.0)	0.1120
Arterial						
Patients	43 (29.9)	27 (26.0)	13 (50.0)	1 (12.5)	2 (33.3)	0.0714†
Events	87	48	36	1	2	
Events per 5 yrs	1.3 (0.8–3.0)	1.2 (0.739–2.93)	1.3 (0.9–1.6)	0.9 (0.9–0.9)	44.7‡ (6.4–83.0)	0.1343
Gastrointestinal						
Patients	11 (7.6)	9 (8.6)	2 (7.7)	–	–	1.000†
Events	13	11	2	–	–	
Events per 5 yrs	1.4 (0.5–1.6)	1.5 (1.3–1.6)	0.4 (0.4–0.4)	–	–	0.0339
Pulmonary						
Patients	11 (7.6)	10 (9.6)	1 (3.8)	–	–	0.904†
Events	17	16	1	–	–	
Events per 5 yrs	1.0 (0.7–1.6)	1.2 (0.7–1.6)	0.9 (0.9–0.9)	–	–	0.7518
Death	17 (11.8)	11 (10.6)	2 (7.7)	2 (25.0)	2 (33.3)	0.1504†

Values are n (%) or median (interquartile range). *Symptomatic events after first work-up (patients with ≥1 event). †Fisher exact test for qualitative variables and Kruskal-Wallis test for quantitative variables. ‡1 arterial event occurred 23 days after the first work-up, explaining a very high number of arterial events per 5 years.

characteristics of the patients between groups defined by the type of medical intervention, except those (n = 8; median age at molecular diagnosis 55.5 years) who were kept on medications other than celiprolol.

Because of the recruitment bias mainly based on initial symptoms or complications for patients with vEDS, index cases had a higher history of previous medical events than their first-degree relatives (82.4% vs. 43.4%; $p < 0.0001$) despite their younger age (33.0 years vs. 41.0 years; $p = 0.0014$) (Online Table 2). A detailed flowchart of the study is given in Online Figure 1. Among the 91 index cases, 19 (20.8%) had a proven de novo mutation and 43 (47.2%) had no suggestive familial history, therefore suggesting a de novo mutation. Among the 258 first-degree relatives, there were 53 patients with proven *COL3A1* pathogenic variants, but we had no access to 47 individuals likely affected with regards to their medical history. Among them, 37 individuals (male/female ratio 20/17) died of a possible vEDS-related cause.

At the initial diagnostic work-up, 74 of the 144 patients (51.4%) had a history of acute arterial event or arterial lesions detected by cardiac computed tomography angiogram and/or Doppler ultrasound, at a median age of 33.0 years (IQR: 27.0 to 40.5 years; min-max: 13.0 to 70.0 years) (**Table 1**). Almost one-quarter (22.7%) reported 2 symptomatic arterial events and 11 (8.3%) patients presented with a third arterial event prior to diagnosis. The most common arterial lesions were dissections (70.1%), followed by aneurysms and false aneurysms (20.4%), arterial ruptures (6.0%), and direct spontaneous carotid cavernous fistula (2.5%). Their most common locations were the abdominal aorta and its branches (gastrointestinal and renal arteries) (37.2%), carotid and vertebral arteries (29.4%), and iliac and femoral arteries (26.6%) (Online Table 3).

MEDICAL INTERVENTION. At the initial work-up, 50% of patients were not treated regularly and only 33.3% were taking celiprolol (Online Table 4). By the end of the study period, almost all patients (90.3%) were treated with celiprolol alone or in combination (Online Figure 2). The proportion of patients taking blockers of the renin-angiotensin system increased with age to a maximum of 20.1%. Common indications necessitating this combination were arterial hypertension and renal ischemia with renovascular hypertension. Once the maximum tolerated dose of celiprolol was reached, 90 (62.5%) patients remained at this dose throughout their follow-up. Only 5 (3.5%) patients required dose reduction due to fatigue, and no serious drug-related adverse event was recorded.

For patients taking celiprolol, the median treatment duration for all patients was 5.2 years (IQR: 3.0 to 7.3 years). During their respective follow-up, 120 of 144 (83.3%) patients were considered adherent to celiprolol at either 400 mg/day (n = 92; 63.9%), or at

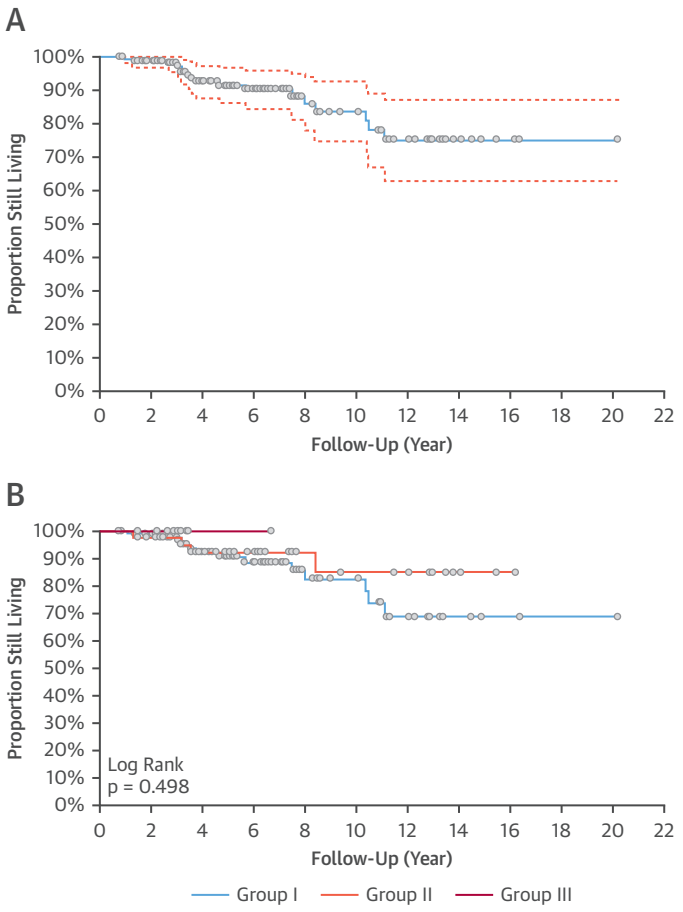
doses <400 mg/day (n = 28; 19.4%). The median dose of celiprolol throughout follow-up was 400 mg/day (IQR: 333 to 400 mg/day) in patients at full dose, and 217 mg/day (IQR: 200 to 300 mg/day) in patients at lower doses. No difference in demographics (sex and age) as well as in the spectrum of *COL3A1* mutations was observed in the patients taking high or low doses of celiprolol. A smaller group of patients (n = 14; 9.7%) were reported to be nonadherent at some point during follow-up, 7 (4.9%) were taking another beta-blocker, and 2 (1.4%) declared themselves intolerant to celiprolol due to fatigue

ARTERIAL EVENTS. A total of 117 clinical events occurred in 53 patients at a median rate of 1.6 events (IQR: 0.9 to 3.0 events) per 5 years, without significant difference between treatment groups (Table 2). A total of 87 new, symptomatic arterial events occurred in 43 patients (<30% of patients). For each of these patients, we observed 1 to 5 new arterial events, with a median of 1.3 events (IQR: 0.3 to 3.0 events) over the 5.3 years follow-up period. The cumulative incidence of a first and second new arterial event during follow-up was 56.8% (95% CI: 50% to 70%) and 29.8% (95% CI: 20% to 50%), respectively. The mean age of occurrence of this first and second new arterial event was 37 (95% CI: 30 to 40) and 48 (95% CI: 40 to 60) years respectively.

During follow-up, all patients with Group III *COL3A1* pathogenic variants remained asymptomatic. However, this group differed from Groups I and II by the high number of relatives (10 relatives for 2 index cases) and their shorter mean duration of follow-up (3.2 vs. 6.3 years, p<0.01). Arterial accidents occurred in Groups I and II, totaling 107 clinical arterial events in 52 patients (39.4%). The arterial progression score distribution at baseline demonstrated that most patients (72.7%) were in the lower progression groups at baseline. At the end of the follow-up, the majority of patients remained in their respective progression groups: very low 75.0% (51 of 68), low 71.4% (20 of 28), and medium 70.0% (21 of 30) progression, indicating clinical stability in more than two-thirds of patients (Online Figure 3).

SURVIVAL. During the same period, 17 (11.8%) patients died at a median age of 35.0 years (IQR: 26.0 to 41.0 years) (Table 2). Arterial rupture was the most common cause of death (n = 12; 70.6%), followed by gastrointestinal perforation (n = 2; 11.8%), with 3 remaining deaths unrelated to vEDS (Online Table 5). Overall, the survival of patients was 99.3% at 1 year, 89.9% at 5 years, and 83.4% at 10 years of follow-up. Overall patient survival was 74.9% (95% CI: 62.7% to 87.0%) (Figure 2A). Due to the low number of deaths, a median age of survival could not be determined. Patient survival did not significantly differ between groups of pathogenic variants, but notably, no deaths occurred in Group III patients (Figure 2B).

FIGURE 2 Kaplan-Meier Survival Analysis of 144 vEDS Patients



(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.

EFFECT OF CELIPROLOL ON SURVIVAL AND ON THE RATE OF HOSPITALIZATIONS. Comparison of deceased patients with survivors is indicated in Table 3. Death occurred only among the 132 patients with Group I and II pathogenic variants, known to be associated with the most severe forms of the disease. A trend for a higher mortality was observed in male versus female patients (hazard ratio [HR]: 2.2;

TABLE 3 Characteristics of Patients Who Died During Follow-Up Compared With Surviving Patients

	Deceased Patients (n = 17)	Alive (n = 127)	p Value
Sex			
Male	9 (52.9)	48 (37.8)	0.2304
Female	8 (47.1)	79 (62.2)	
Age at the beginning of the follow-up	28.0 (21.0–38.0)	35.0 (26.0–43.0)	0.0765
Age at death or at the last follow-up	35.0 (26.0–41.0)	41.0 (33.0–50.0)	0.0496
Status			
Index case	13 (76.5)	78 (61.4)	0.2268
Relative	4 (23.5)	49 (38.6)	
Type of variant			
Group I	13 (76.5)	77 (60.6)	0.4318*
Group II	4 (23.5)	38 (29.9)	
Group III	0 (0.0)	12 (9.5)	
Treatment with celiprolol			
Yes	9 (52.9)	111 (87.4)	0.0017
No	8 (47.1)	16 (12.6)	

Values are n (%) or median (interquartile range). *Chi-square test for Group I versus Group II.

p = 0.102) but this was not significant, possibly because of a relatively low number (n = 17) of deaths. The mortality was much higher in subjects age <34 years (HR: 20.0; p = 0.0002). Of 17 deaths, 8 (47.1%) patients were not treated, compared with 16 (12.6%) among the 127 subjects alive (p = 0.0017).

Survival curve analysis showed that those not treated with celiprolol had a significantly worse outcome than treated patients (**Figure 3A**): survival was 80.7% (95% CI: 67.8% to 93.6%) in those treated with celiprolol versus 48.5% (95% CI: 19.7% to 77.4%) in those not treated (p < 0.001) after 11.1 years of follow-up. It is important to note that our celiprolol-treated group was not older, and if anything, rather younger than the others (**Table 1**). When the patients taking celiprolol only were considered (n = 110), survival was significantly higher in patients taking celiprolol 400 mg/day (n = 83) than in patients taking 100 to 300 mg/day (n = 27) (**Figure 3B**).

The cumulative number of hospitalizations during the whole study period was also analyzed. Hospitalizations for both symptomatic arterial accidents and arterial monitoring in asymptomatic patients paralleled hospitalizations for the total number of patients (Online Figure 4). Interestingly, despite no change in patient monitoring standards along with a constant increase in patients followed by our center, the hospitalization rates stabilized with the prescription of celiprolol starting in 2011. Notably, we observed a statistically significant difference in the ratio of hospitalizations for acute arterial events/hospitalizations for regular follow-up before and after 2011 (odds ratio: 1.7; 95% CI: 1.1 to 2.8; p = 0.0257), suggesting a positive effect of celiprolol on the severity of these new arterial events (**Table 4**). These findings may however be influenced by other factors, such as a higher proportion of affected relatives and a shorter follow-up period for patients included after 2011.

DISCUSSION

This study is, to the best of our knowledge, the only additional study following the BBEST trial to provide an extensive report of pharmacological treatment and outcomes in a unique, large, and systematically screened and recorded cohort of patients with vEDS. Our findings indicate that patients followed in our referral center had a lower mortality than that expected from the natural history of the disease described in previous North American reports (4,8). Our comparison with the 2 overlapping reports of the U.S. vEDS population is, however, limited by the lack of information of the survival starting at the age of 18 years given in these 2 studies (Pepin 2010 and 2014). In fact, during this average 5.3 years of follow-up, the survival rate was 71.6% in the entire vEDS cohort, a rate that would even increase to 80% if those who died of non-vEDS-related causes were excluded (**Central Illustration**). Given the limited number of deaths, an estimate of median life expectancy in treated patients was not possible. This high survival rate was influenced mainly by the age at which the diagnosis was made and the type of *COL3A1* pathogenic variants. The role of celiprolol in improved survival cannot be determined from this study, because 90% of the patients were taking celiprolol and all patients were offered this therapy.

Several factors might have further influenced this high survival rate. A first classical confounding factor would be a recruitment bias toward milder forms of the disease (4), which here seems very unlikely. Most (82.4%) of the 91 index cases (63.2% of the cohort) had experienced a major complication at a mean age of 33 years (95% CI: 25.0 to 38.0 years), demonstrating the severity of the disease. This proportion of index patients was higher than that of the North American cohort (52.5%) reported in 2000, thus not driving our study to more moderate or late forms of the disease. The proportions of type of first complication (arterial, gastrointestinal, other organ) were also not different from that reported by Pepin et al. (4), with roughly two-thirds due to arterial events.

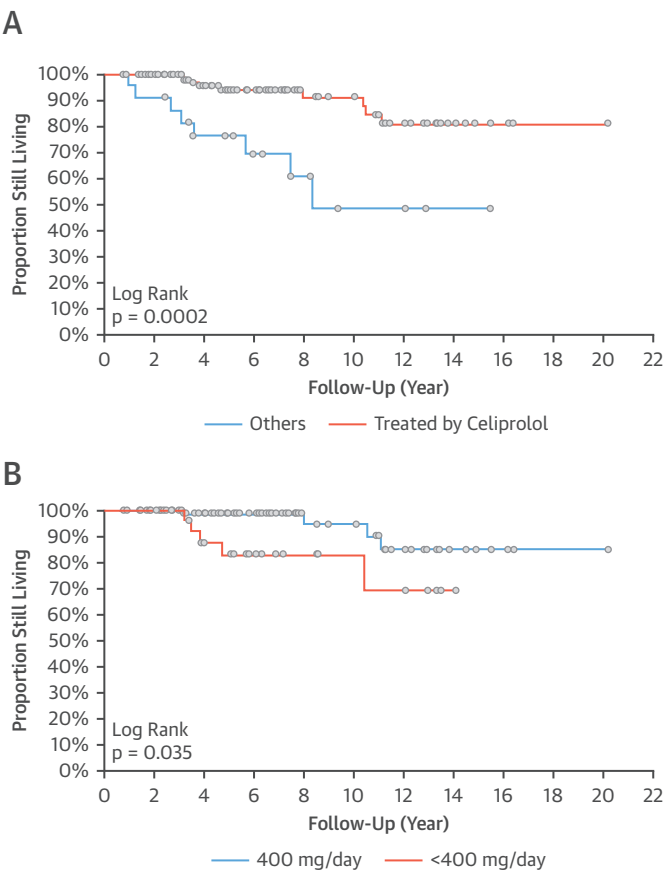
A bias in the type of *COL3A1* pathogenic variant can also be excluded. In contrast to the BBEST study, all patients reported here had molecularly proven vEDS

with pathogenic variants in the *COL3A1* gene (Online Tables 6 and 7) (11). There was a low frequency of patients (n = 12 of 144) with variants leading to haploinsufficiency, the milder form of the disease (3,9). In fact, there was a 100% survival rate in the 2 index cases and 10 relatives with this type of pathogenic variant in a median 3.1 years (range 1.5 to 6.7 years) follow-up. When we restricted the analysis to the 132 patients with either glycine or splice variants, there was still a high survival rate (70%; 95% CI: 50% to 90%) during a median 5.8 years follow-up.

This improvement in survival rate compared with what was expected from the published data could also be favored by the organization of health care for rare diseases in France (13). Since instituting the first national plan for rare diseases, the general policy has been the selection and funding by the French Ministry of Health of 1 national referral center for a particular type of rare disease. Our center for rare vascular diseases was launched in 2006 together with a network of expert centers scattered throughout the country, thus making rapid access to expert physicians easier. Rapid access to care is a key factor in reducing delay in diagnosis and applying the best-known medical practices. For vEDS, our center applies the national and international guidelines of care, especially preventive measures avoiding iatrogenesis and risk factors for major complications in addition to providing medical therapy (8). Whether this general strategy of care has strongly influenced the rate of complications and survival rate is difficult to estimate in the absence of a control group. It is also noteworthy that our standards of care did not change since the year 2000, favoring medical management of acute arterial events whenever possible. During this survey, among the 80 hospitalizations for acute arterial event, only 17 arterial events required an intervention: 10 embolization procedures, 3 open repairs, and 4 endovascular procedures. Thus, technical improvement such as covered stents for arterial ruptures (n = 3) are unlikely to have had a significant effect on overall mortality.

The final and likely most important factor regarding the arterial events and deaths is the pharmacological treatment with celiprolol. Prior to this report, no trial other than the BBEST trial had been published in this rare disease. The BBEST study demonstrated a 3-fold greater reduction in arterial events (rupture or dissection) in celiprolol-treated patients than in untreated patients (11). However, because of several limitations (open trial, limited number of molecularly proven vEDS, unusual molecule not representing a classical type of beta-blocker), the benefits of celiprolol for vEDS patients have been

FIGURE 3 Kaplan-Meier Survival Analysis of vEDS Patients in Groups I and II *COL3A1* Pathogenic Variants, According to Celiprolol Treatment



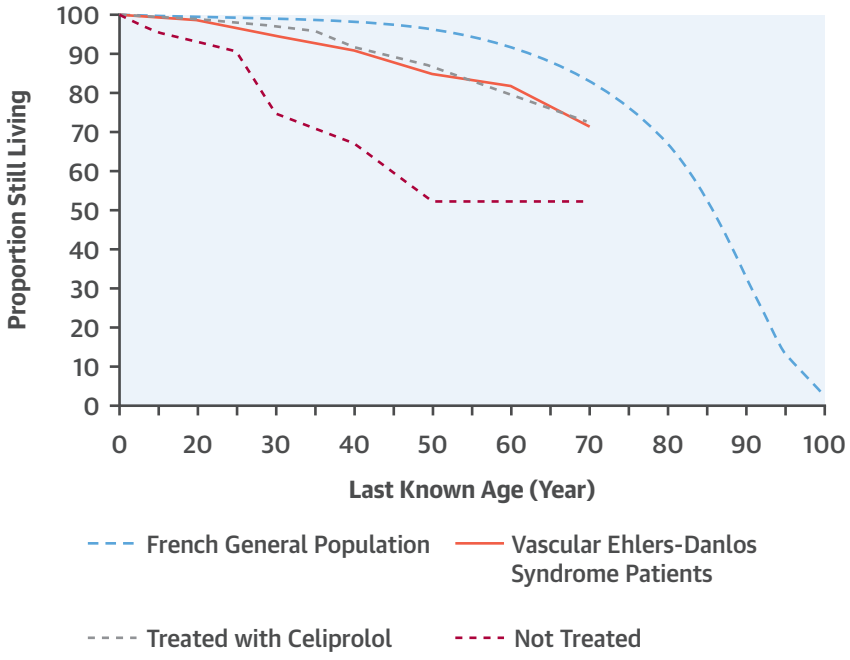
(A) Patients treated with celiprolol versus patients not treated with celiprolol (others). Patients not treated with celiprolol had a significantly worse outcome than treated patients. At the end of follow-up, survival was 80.7% (95% CI: 67.8% to 93.6%) in those treated with celiprolol versus 48.5% (95% CI: 19.7% to 77.4%) in those not treated. Log-rank: treated with celiprolol (n = 110) versus others (n = 22), p = 0.0002 (Others: no treatment [n = 6], nonadherence or intolerance to celiprolol [n = 10], or treated with another drug than celiprolol [n = 6]). **(B)** Survival according to the daily dose of celiprolol. Only patients treated with celiprolol alone were considered (n = 110). At the end of follow-up, survival was 85% (95% CI: 70.5% to 99.5%) in those patients treated with celiprolol 400 mg/day and 69.2% (95% CI: 41.4% to 97.0%) in those taking celiprolol 100 to 300 mg/day. Log-rank survival analysis between the 2 groups: p = 0.035. Abbreviations as in Figure 2.

TABLE 4 Hospitalizations for Acute Arterial Events Before and After the Systematic Introduction of Celiprolol

	≤2011	>2011
Hospitalization for acute arterial event	41 (17.7)	39 (11.2)
Follow-up hospitalization	190 (82.3)	310 (88.8)

Values are n (%). There is a statistically significant difference between the number of hospitalizations for acute arterial event before and after 2011 and until 2017 (odds ratio: 1.7; 95% confidence interval: 1.1 to 2.8; p = 0.0257). This finding suggests a positive effect of celiprolol on the severity of new arterial events.

CENTRAL ILLUSTRATION Comparing Survival of Patients With Vascular Ehlers-Danlos Syndrome in the 2015 French Population



Frank, M. et al. J Am Coll Cardiol. 2019;73(15):1948–57.

Overall patient survival does not reflect the severity and high mortality of vascular Ehlers-Danlos syndrome as it is expected from the natural history of the disease. A major determinant of patient survival is medical treatment with celiprolol.

disputed (8). This drug was chosen because of its vasodilatory properties due to β1-antagonist and β2-partial agonist properties that might be of interest in these patients with increased arterial wall stress (14,15). In the present follow-up study, patient survival was independently associated with treatment by celiprolol, regardless of index/relative status and type of disease-causing variant. Even when restricted to the patients with the most severe types of pathogenic variants, the effect of celiprolol was significant; patients not treated with celiprolol demonstrated a significantly worse outcome than treated patients (survival 72.4% vs. 52.2% respectively; $p < 0.001$). It is noteworthy that neither death nor symptomatic arterial events occurred during follow-up (average 3.2 years) of the 12 patients with variants leading to haplo-insufficiency. This absence of events may be the result of the mild form of vEDS itself, but may also suggest the silencing of the disease by celiprolol treatment. Given the delayed onset of arterial events in this category of patients, further follow-up of a larger number of treated patients with null mutations is necessary.

Survival was significantly improved in patients taking celiprolol 400 mg/day compared with patients taking lower doses, suggesting a dose effect and that 400 mg/day should be considered the optimal treatment dose. Patient adherence to treatment, notably staging of patients as nonadherent to celiprolol, relied on patient interview only. However, these assessments were made in the initial phase of patient care and throughout their follow-up, independently of clinical events or death. Therefore, it is unlikely that this subjective assessment of patient adherence may have significantly influenced outcome measures. However, since this survey was not a randomized trial, there is no doubt that some other confounding factors might have played a role in survival.

Finally, we observed a reduction of the ratio hospitalizations for acute arterial events over those for regular surveillance after the year 2011 (11.2% vs. 17.7%; $p = 0.025$), corresponding to the systematic introduction of celiprolol whenever possible and accepted. This is an indirect argument for a possible effect of the drug on the occurrence and/or severity of the disease, especially when considering the

suggested dose effect of celiprolol on survival. It is difficult to formally assess this beneficial effect in the absence of a placebo-controlled prospective trial, because other confounders might have influenced this observation (8). In that regard, it can be argued that there is still no study that definitively proves that celiprolol affects mortality or vascular events.

STUDY LIMITATIONS. This retrospective observational study included all vEDS patients followed by our center. Nonetheless, the monocentric setting of this study limits the generalization of our findings, because specific management procedures in a dedicated center for vEDS patients may have influenced patient outcome. Second, given the longitudinal nature of this follow-up and the absence of a control group, the reduction of arterial events by celiprolol cannot be formally documented.

CONCLUSIONS

The analysis of this unique large cohort carefully followed in a referral center demonstrates a better prognosis than expected from the natural history of vEDS.

ADDRESS FOR CORRESPONDENCE: Dr. Xavier Jeunemaitre, National Referral Center for Rare Vascular Diseases, Hôpital Européen Georges Pompidou, AP-HP, 20-40, rue Leblanc, 75015 Paris, France. E-mail: xavier.jeunemaitre@aphp.fr. Twitter: @HopitalPompidou.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with vEDS, a pathogenic variant of *COL3A1* may be associated with a salutary response to celiprolol.

TRANSLATIONAL OUTLOOK: Long-term, multicenter follow-up studies should be undertaken to more completely characterize outcomes of this and other types of drug therapy for patients affected with this rare disease.

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KEY WORDS *COL3A1*, celiprolol, drug therapy, Ehlers-Danlos syndrome, survival, vascular type

APPENDIX For supplemental figures, tables, and references, please see the online version of this paper.