Circulation

ORIGINAL RESEARCH ARTICLE

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; Mohamed El Hachmi, MSGC; Alessandra Bura-Rivière, MD, PhD; François-Xavier Lapébie, MD, PhD; Claire Le Hello, MD, PhD; Damien Laneelle, MD, PhD; Christophe Seinturier, MD; Klaus Dieterich, MD, PhD; Marc Lambert, MD, PhD; Sophie Dupuis-Girod, MD, PhD; Stéphane Zuily, MD, PhD; Laurence Bal-Theoleyre, MD; Carine Boulon, MD; Pierrick Henneton, MD; Estelle Lu, MStat; Nicolas Denarié, MD; Pierre Boutouyrie, MD, PhD; Tristan Mirault, MD, PhD; Gilles Chatellier, MD, PhD; Michel Azizi, MD, PhD

BACKGROUND: Vascular Ehlers-Danlos syndrome is a rare genetic disorder characterized by defective type III collagen and a high risk of arterial morbidity and mortality. Several cardiovascular drugs are used for treatment, including celiprolol, but no controlled trial in this condition has been conducted to date. We hypothesized the benefit of the addition of an angiotensin II receptor blocker.

METHODS: A multicenter, randomized, placebo-controlled trial was conducted to assess the efficacy and safety of the angiotensin II receptor blocker irbesartan in adults with vascular Ehlers-Danlos syndrome on stable background celiprolol therapy. Patients were randomized 1:1 to receive irbesartan (150 mg/day titrated to 300 mg/day) or placebo for 2 years. The composite primary outcome was defined as any vascular Ehlers-Danlos syndrome–related fatal or nonfatal arterial event or any new or worsening arterial lesions detected by systematic head-to-pelvis computed tomography angiography or peripheral arterial duplex ultrasound at different time points, using a time-to-first-event analysis.

RESULTS: Twenty-nine participants (62% female; 40.3±11.3 years of age) were randomized to irbesartan, and 28 (64% female; 40.7±11.0 years of age) were randomized to 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. Irbesartan significantly reduced systolic blood pressure compared with placebo (baseline-adjusted difference of 5.4 mm Hg [$P<0.001$]), but no relation was observed with the reduction of the primary composite outcome. Eleven episodes of irbesartan-related hypotension were recorded, leading to a downtitration in 4 patients.

CONCLUSIONS: 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.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02597361.

Key Words: angiotensin receptor antagonists ■ celiprolol ■ collagen ■ computed tomography angiography ■ Ehlers-Danlos syndrome, type IV

Vascular Ehlers-Danlos syndrome (VEDS) is a rare genetic disorder caused by variants in the *COL3A1* gene that result in a defect in type III collagen, leading to fragility of the extracellular matrix (OMIM 130050). This susceptibility to mechanical stress is a challenge in the management of the disease, because

Correspondence to: Xavier Jeunemaitre, MD, PhD, Hôpital Européen Georges Pompidou, Service de Médecine Génomique des Maladies Rares et DMU BIOPHYGEN, F-75015, Paris, France. Email xavier.jeunemaitre@aphp.fr

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.124.072849.
For Sources of Funding and Disclosures, see page XXX.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- Several cardiovascular drugs have been used to prevent arterial rupture or dissection in patients with vascular Ehlers-Danlos syndrome, but no controlled trial has been conducted.
- The ARCADE trial (Angiotensin II Receptor Blockade in Vascular Ehlers-Danlos Syndrome) was designed to test the hypothesis of a beneficial effect of adding an angiotensin II receptor blocker to celiprolol, the reference beta-blocker used in this condition.
- Compared with placebo, irbesartan, a long-acting angiotensin II receptor blocker, reduced the incidence of new symptomatic and asymptomatic arterial events by 50% over a 2-year period, with no side effects other than hypotension.

What Are the Clinical Implications?

- The substantial and consistent beneficial effects of irbesartan across the various arterial end points analyzed in this study support the systematic consideration of an angiotensin II receptor blocker in the treatment of patients with vascular Ehlers-Danlos syndrome to prevent arterial events.
- Irbesartan is not only known for its safety profile, but is also available as a low-cost generic drug, making it an advantageous option for the treatment of this rare disease.
- The results of this first randomized controlled trial are expected to have a direct and important impact on the medical management of this life-threatening condition.

Nonstandard Abbreviations and Acronyms

ARB	angiotensin II receptor blocker
ARCADE	Angiotensin II Receptor Blockade in Vascular Ehlers-Danlos Syndrome
BBEST	Beta-Blockers in Ehlers-Danlos Syndrome Treatment
BP	blood pressure
CTA	computed tomography angiography
DN	dominant negative
DUS	duplex ultrasound
HR	hazard ratio
VEDS	vascular Ehlers-Danlos syndrome

patients with VEDS are prone to life-threatening complications, such as spontaneous arterial dissection, rupture, and bowel perforation.[1,2] Despite advances in medical management, patients with VEDS remain at high risk of morbidity and mortality, with arterial ruptures a leading cause of adverse events.[3–6]

Several cardiovascular drugs are used to prevent vascular events,[4,5,7] although the level of evidence is low, as no randomized placebo-controlled trials have ever been conducted. Celiprolol, a beta-blocker with vasodilator activity, showed a significant reduction in major fatal and nonfatal vascular events in the open-label randomized BBEST trial (Beta-Blockers in Ehlers-Danlos Syndrome Treatment)[8] and in 2 observational studies.[3,9] Despite optimized medical management, patients with VEDS continue to develop new symptomatic and asymptomatic arterial lesions,[3,10] a persistent disease process that justifies the investigation of additional therapeutic approaches.

Both our findings from col3a1 mouse models of VEDS[11,12] and the benefits observed in Marfan syndrome, another connective tissue disease that predisposes to aortic rupture,[13] support investigating the potential efficacy of angiotensin II receptor blockers (ARBs) in preventing vascular events in patients with VEDS. We therefore designed a proof-of-concept study to assess the efficacy and safety of a long-acting ARB, irbesartan, in reducing vascular events in patients with VEDS on background therapy with celiprolol.

METHODS

Data Sharing

The data are held by Assistance Publique–Hôpitaux de Paris, France. Data sharing must be accepted by the sponsor Assistance Publique–Hôpitaux de Paris and the principal investigator based on scientific project and scientific involvement of the principal investigator team. Applications to share the deidentified and anonymized trial data with other investigators for use in future research will be considered, subject to review of the aims and scientific methods of the application, and any contractual obligations required by organizations involved in the study. Requests for data sharing or collaboration should be made to the corresponding author. Teams wishing to obtain individual participant data must meet the sponsor and principal investigator team to present scientific (and commercial) purpose, individual participant data needed, format of data transmission, and timeframe. Technical feasibility and financial support will be discussed before mandatory data access agreement. Processing of shared data must comply with the European general data protection regulation.

Trial Oversight

The French multicenter, randomized, double-blind, placebo-controlled ARCADE trial (Angiotensin II Receptor Blockade in Vascular Ehlers-Danlos Syndrome) was conducted at 10 referral centers of the Rare Vascular Diseases network in France (Supplemental Material). The trial was approved by the Comité de Protection des Personnes Paris Ile de France IV. All patients provided written informed consent. The protocol was defined by the executive committee. The clinical research unit of the Hôpital Européen Georges Pompidou (E.L., G.C.) was responsible for data collection, monitoring, and analysis. The authors had full access to the data and statistical analyses. The authors had

full responsibility for the decision to submit for publication. The study was funded by a grant from the French Ministry of Health (PHRC 140918) and sponsored by the Assistance Publique–Hôpitaux de Paris. The trial is registered (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02597361).

Patients

Eligible participants were men or women 18 to 70 years of age with a pathogenic variant of the *COL3A1* gene, treatment with celiprolol for ≥12 weeks before randomization, and an estimated glomerular filtration rate of ≥30 mL·min·1.73 m^2. The main exclusion criterion was an ongoing life-threatening VEDS-related complication (see page 4 of the Supplemental Material for full inclusion and exclusion criteria).

After acceptance of eligibility, patients entered a 4- to 12-week prerandomization period during which background celiprolol treatment was titrated up to 400 mg daily if tolerated. Patients also underwent baseline head-to-pelvis computed tomography angiography (CTA) and peripheral artery duplex ultrasound (DUS). They were then randomized (1:1) to receive either irbesartan or a placebo for 24 months. The starting dose of irbesartan or placebo was 150 mg per day, with an increase to 300 mg (2× 150-mg tablets) over 8 weeks as tolerated. In the event of intolerance, the dose of irbesartan or matching placebo could be temporarily reduced or stopped. Changes in the celiprolol dose and the prescription of other renin-angiotensin-aldosterone system blockers were prohibited.

Patients were seen at monthly visits for the first 3 months and then at 6, 12, 18, and 24 months for clinical and safety assessments. Physical examination, supine and standing office blood pressure (BP) and heart rate, medication lists, and adverse events were recorded. Laboratory tests were performed at each visit. Head-to-pelvis CTA was performed at baseline and at 12 and 24 months using the reference imaging modality for all major arterial territories except distal limb arteries, which were assessed using DUS at baseline and at 6, 12, 18, and 24 months. The radiologists at each center were responsible for selecting the appropriate acquisition technique and quantity of contrast medium. One stipulation was the necessity for a computed tomography system with a minimum of 64 rows to guarantee the inclusion of sections with a thickness <1 mm, encompassing all arterial axes. CTA images were sent to a core laboratory for evaluation of the quality of the examination and assessment of changes from baseline in arterial lesions by the imaging committee, blinded to treatment assignment (Supplemental Material).

Randomization and Blinding

Patients were assigned to irbesartan or placebo (1:1) through a web-based procedure, using a computer-generated block randomization stratified by center and type of *COL3A1* variant (dominant negative mechanism versus haploinsufficiency).

Outcomes

The 24-month primary efficacy outcome was the composite of cardiovascular death or any VEDS-related fatal or nonfatal event as adjudicated by the event committee and either new asymptomatic arterial aneurysms or dissections or worsening of a preexisting lesion (dissection, aneurysm, or contained limited rupture; Figures S1 and S2). Symptomatic vascular events included arterial dissections of any type, aneurysms, ruptures, and arteriovenous fistulae. Iatrogenic arterial complications were excluded (Supplemental Material).

Key secondary efficacy outcomes included 24-month incidence of each component of the composite primary outcome, number of arterial lesions on the 12- and 24-month imaging, time to first symptomatic cardiovascular event, 24-month incidence of any symptomatic VEDS-related nonvascular event (gastrointestinal, pulmonary, or other), incidence of unplanned hospitalization for any VEDS-related event (vascular or nonvascular), change in office systolic and diastolic BP from baseline, and safety outcomes.

Two committees, both independent of the investigators and unaware of the treatment allocation, were responsible for adjudicating the symptomatic and asymptomatic outcomes (Supplemental Material). The end point adjudication committee consisted of 3 experts, operating in an independent capacity from that of the investigators. The imaging committee was tasked with analyzing each arterial segment. All CTA images were analyzed by a minimum of 2 experts. New asymptomatic arterial lesions or progressing preexisting lesions were further adjudicated by the imaging committee over the course of the 24-month follow-up period. A total of 70 clinical and imaging events (n=28 in the irbesartan group; n=42 in the placebo group) were ultimately adjudicated by these 2 committees.

Statistical Analysis

For the primary efficacy outcome, we determined that a sample size of 54 patients per group would have 80% power (with a 2-sided α risk of 5%) to reject the null hypothesis of no difference between groups, assuming an event rate of 20% and 45% in the irbesartan and placebo groups, respectively (Supplemental Material). Because of a lower-than-expected rate of patient recruitment over 2 years, both the steering committee and the study sponsor decided to stop enrolling patients on March 31, 2018. Because the rate of the primary symptomatic outcome was lower than expected, the planned interim analysis was not performed.

All analyses were conducted on an intention-to-treat basis. The incidence of clinical events and other categorical data are summarized as percentages. Continuous data are presented as means (±SD) or medians and interquartile ranges. Kaplan-Meier plots were constructed for time-to-event outcomes, with treatment effects estimated using Cox models and results presented as a hazard ratio (HR) with 95% CI. For the primary outcome, to account for the recurrence of arterial symptomatic or asymptomatic events per individual, statistical significance was assessed using both a Cox model and a Poisson regression model.

Secondary outcomes are presented with effect size estimates and 95% CI. The 95% CI widths were not adjusted for multiplicity; any inferences drawn from these intervals may not be reproducible.

Between-group differences in BP from baseline to 24 months were assessed using linear mixed models with adjustment on the initial BP value (Supplemental Material). Planned subgroup analyses of the primary outcome were performed by age, sex, and genetic status (variants and family). Statistical analyses were performed using SAS (version 9.2) and R (version 4.0.2) software.

RESULTS

From January 21, 2016, to March 30, 2018, 61 patients were enrolled, and 57 were randomized to either the irbesartan (n=29) or placebo (n=28) group (Figure 1). Study groups were similar in baseline demographic, clinical, biological, and imaging characteristics (Table 1; Table S1). As expected, the pathogenic variants at the *COL3A1* gene were found mainly to act through a dominant negative (DN) mechanism (Table S2). Most patients had a history of VEDS-related complications. At baseline, 48 patients (84.2%; Table 1)[14] had arterial lesions in any vascular bed. From week 8, >80% of patients were receiving the maximum dose of 300 mg per day of irbesartan, with a stable daily dose of celiprolol in both groups (Table 2).

The Kaplan-Meier event-free survival curve showed that the incidence of the primary composite outcome was lower in the irbesartan group than in the placebo group (Cox model; HR, 0.42 [95% CI, 0.17, 0.99]; Figure 2). No fatalities occurred. The 9 symptomatic arterial events were arterial dissections (n=8) and aneurysm rupture (n=1). They occurred later with irbesartan (n=3; mean 21.8 months) than with placebo (n=6; mean 14.2 months; Figure S3; Table S3).

When we considered only new arterial asymptomatic lesions (new lesion or progression of a preexisting lesion detected by CTA), their total number was significantly reduced by irbesartan compared with placebo both at 2 years and already at 1 year (Table 3). This reduction of

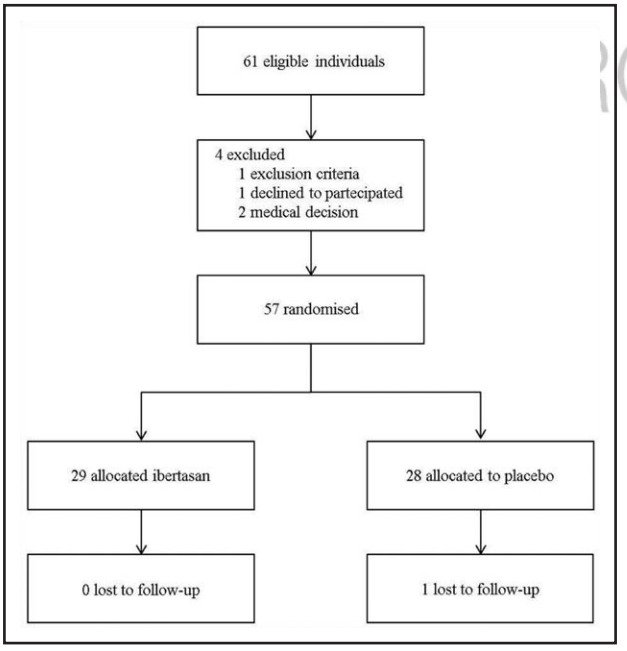

Figure 1. Flowchart of the study.
Four exclusions occurred between enrollment and randomization: 2 medical decisions (2 cases of renal artery dissection), 1 exclusion criterion (discovery of pulmonary embolism at computed tomography angiography), and 1 loss to follow-up after inclusion.

Table 1. Baseline Characteristics at Randomization

Characteristics*	Irbesartan (n=29)	Placebo (n=28)
Male sex	11 (38.9)	10 (35.7)
Age, y	41.0±11.2	41.3±10.9
Weight, kg	60.7±9.8	65.2±13.8
Height, cm	164±9	167 ±9
Body mass index, kg/m^2	22.5 ±3.2	23.2±4.0
Systolic BP, mm Hg	117.2±9.6	121.7 ±9.9
Diastolic BP, mm Hg	68.5±8.9	73.9±9.3
Heart rate, bpm	67.9 ±9.5	70.1 ±8.8
Renal function		
Plasma creatinine, µmol/L	70.0±13.0	73.6±13.7
eGFR, mL·min·1.73 m^2†	100.9±24.7	95.4±22.8
Genetics		
*COL3A1*gene variant‡		
Glycine missense	23 (79.3)	13 (46.3)
Splice site	4 (13.8)	9 (32.1)
Stop, indel, frameshift	2 (6.9)	6 (21.4)
Family genetic status§		
Index	19 (65.5)	18 (64.3)
Relatives	10 (34.5)	10 (35.7)
VEDS symptomatic history		
Arterial event	24 (82.8)	24 (85.7)
Digestive event	8 (27.6)	6 (21.4)
Pulmonary event	4 (13.8)	2 (7.1)
Obstetric event‖	3 (16.7)	0 (0)
Treatment with celiprolol		
Average daily dose, mg#	317.9±102.0	360.7 ±103.1
Dose range: 100–200 mg	10 (34.7)	4 (14.3)
Dose range: 300–400 mg	18 (64.3)	24 (85.7)
Cardiovascular risk factors		
Arterial hypertension	0 (0)	2 (7.1)
Type 2 diabetes	0 (0)	1 (3.6)
Dyslipidemia	5 (17.2)	8 (28.6)
Smoking status		
Ongoing	2 (6.9)	2 (7.1)
Past	7 (24.1)	7 (25.0)
Arterial lesions		
Any	24 (82.8)	23 (82.1)
Supra-aortic	22 (75.9)	20 (71.4)
Visceral	18 (62.1)	17 (60.7)
Iliofemoral	17 (58.6)	12 (42.9)

Data are expressed as n (%) or mean±SD. BP indicates blood pressure.

*Baseline characteristics did not differ significantly (P<0.05) between randomization groups.

†Estimated glomerular filtration rate (eGFR) is calculated with the Modification of Diet in Renal Disease equation formula Chronic Kidney Disease Epidemiology Collaboration.[14]

‡Three types of *COL3A1* heterozygous variants are reported: (1) missense variant on a glycine residue; (2) splice variants, both of them acting with a dominant negative mechanism; or (3) stop variant, insertion/deletion (indel), or frameshift variant resulting in the translation of the genetic code in an unnatural reading frame, leading to haploinsufficiency. One variant initially classified as dominant negative at inclusion (in the placebo group) was reclassified as haploinsufficiency during the analysis of the study (Table S2).

§Patients were classified as index cases if they were the initial patients identified within a specific family and as relatives if they belonged to a vascular Ehlers-Danlos syndrome (VEDS) family initially identified through an index case. The relatives enrolled in the study belonged to families independent of the recruited index cases.

‖Percentage of obstetric events calculated out of 18 women in each group.

#One patient did not receive celiprolol throughout the trial because of previous drug intolerance, and one patient was taking 600 mg daily of celiprolol.

Table 2. Blood Pressure, Heart Rate, and Treatment Status During the Trial

BP and heart rate	Irbesartan (n=29)	Placebo (n=28)	*P* value
At randomization			
Celiprolol, mg/d	317.9±102.0	360.7±103.1	0.122
Dose (irbesartan/placebo)			
Systolic BP	117.2±9.6	121.7±9.9	0.089
Diastolic BP	68.5±8.9	73.9±9.3	0.028
Heart rate	67.9±9.1	70.1±8.8	0.358
At 2 mo* (visit 3)			
Dose 1/day	7 (24.1)	2 (7.7)	
Dose 2/day	22 (75.9)	24 (92.3)	
Systolic BP	109.4±8.9	118.9±9.2	<0.001
Diastolic BP	63.5±8.5	73.0±9.7	<0.001
Heart rate	71.5±10.9	71.8±9.3	0.907
At 6 mo (visit 5)			
Dose 1/day	5 (18.5)	3 (12.0)	
Dose 2/day	22 (81.5)	22 (88.0)	
Systolic BP	107.9±8.6	119.3±8.7	<0.001
Diastolic BP	63.6±8.1	71.4±10.0	0.002
Heart rate	70.2±10.8	70.3±8.0	0.978
At 1 y (visit 7)			
Dose 1/day	5 (18.5)	3 (12.0)	
Dose 2/day	22 (81.5)	22 (88.0)	
Systolic BP	110.7±9.7	118.0±7.7	0.003
Diastolic BP	65.5±8.7	70.3±9.8	0.059
Heart rate	70.9±11.4	69.4±7.0	0.534
At 2 y (visit 11)			
Celiprolol mg/d	322±109	352±101	0.256
Dose 1/day	4 (16)	2 (8.7)	
Dose 2/day	21 (84)	21 (91.3)	
Systolic BP	111.9±8.6	116.6±7.9	0.039
Diastolic BP	65.4±7.7	70.7±8.9	0.021
Heart rate	69.9±9.1	71.3±7.5	0.528

Data presented as mean±SD or n (%). Blood pressure (BP) values are in mm Hg and heart rate values are in pulse per minute.

*Few missing values for the record of whether the patient was on dose 1 or dose 2 at one or the other visit.

progression was observed mainly at the visceral arteries (Table S4). When all arterial lesions detected by CTA from baseline to 2 years were considered, there was an increase in the number of lesions in all arterial sites only in the placebo group (Table S5).

During the 2-year period, the recurrence rate of both symptomatic and asymptomatic events per patient was lower in the irbesartan group (13 events among 29 patients) than in the placebo group (35 events among 28 patients; Figure 3). Using a Poisson distribution to account for the number of events per individual patient, we found a relative risk of 0.37 (95% CI, 0.19, 0.68; *P*=0.002) in favor of irbesartan.

A significant reduction in both systolic and diastolic BP was observed from the end of the titration period to the end of the study compared with placebo (Table 2; Figure 4). The baseline-adjusted between-group difference in systolic and diastolic BP in favor of irbesartan was −5.4 mm Hg (95% CI, −7.8, −3.0; *P*<0.001; Table S5) and −4.1 mm Hg (95% CI, −6.9, −1.3; *P*<0.005; Table S6), respectively. No significant changes in heart rate occurred in either group (Table S7). There was no association between the reduction in BP observed with irbesartan and the occurrence of the primary composite outcome, either when the mean reduction in BP was analyzed (Table S8) or when the individual data were analyzed (Figure S4).

Age, sex, whether the patient is the index case or a relative, and the type of genetic variant are factors that may influence the occurrence of arterial complications in patients with VEDS. The Cox proportional hazards models for the occurrence of the primary composite outcome were consistent across all subgroups (Figure 5), with a trend toward greater efficacy for irbesartan in men. Patients with a high number of arterial lesions at baseline had the worst outcome at 24 months, but the effect of irbesartan versus placebo was independent of this measure in a post hoc analysis (Figure S5).

The full list of serious adverse events is shown in Table S9, and the expected drug-related clinical and biological adverse effects are shown in Tables S10 and S11. In the irbesartan group, 4 women had symptomatic hypotension, leading to downtitration in 3 of them, and 9 patients (2 men and 7 women [31.0%]) had a systolic BP <100 mm Hg at least once during the 2-year study (no discontinuation; one downtitration). Of note, 4 patients with preexisting varicose veins (3 on irbesartan and one on placebo) had venous thromboembolism episodes at baseline or during follow-up. There were 2 reversible episodes of mild hyperkalemia (>5 mmol/L) in both groups and 4 episodes of reversible estimated glomerular filtration rate increase >20% in the irbesartan group versus 2 in the placebo group.

DISCUSSION

Patients with VEDS are at high risk of cardiovascular morbidity and mortality. Their life expectancy historically has been estimated to be severely limited, highlighting the need for effective therapeutic interventions.[2] In this first multicenter, randomized, double-blind, placebo-controlled trial, we observed a high rate (17.9%) of symptomatic arterial events over 2 years in the placebo group treated only with celiprolol compared with the rate of fatal and nonfatal arterial events over 47 months in the previous

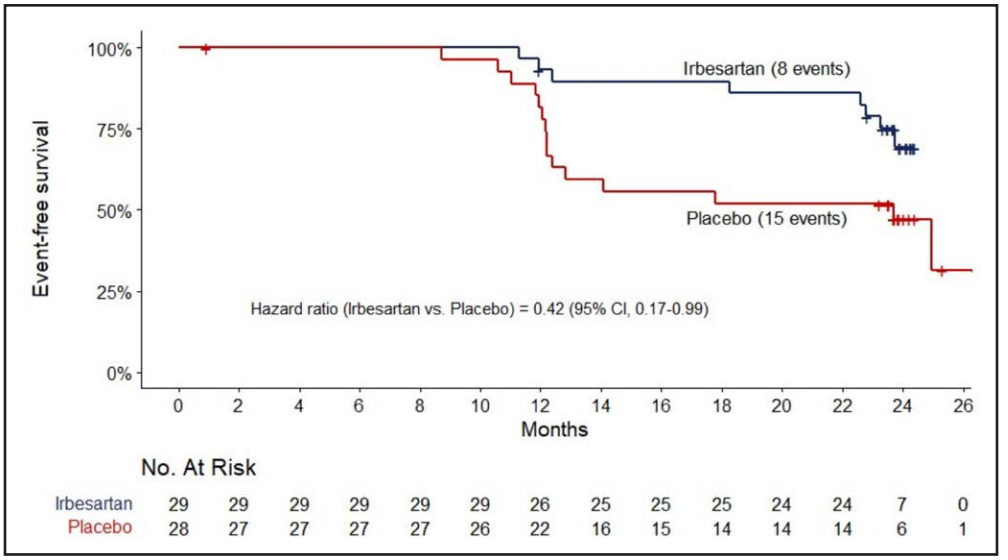

Figure 2. Occurrence of primary composite end points during the 2-year study.

open-label BBEST trial (20%).[8] Irbesartan in combination with celiprolol significantly reduced the occurrence and recurrence of both symptomatic events (including arterial dissections and ruptures) and asymptomatic arterial lesions (mainly localized arterial dissections and aneurysms) at all arterial sites. Irbesartan also delayed the onset of clinical events and the detection of new arterial lesions.

Lowering BP is of paramount importance in the prevention of aortic aneurysms and the reduction of overall cardiovascular risk.[15] Pulsatile arterial BP is a major stress factor for the arterial wall in patients with VEDS, who have weakened arterial walls due to defective type III collagen.[16,17] In the ARCADE trial, patients with VEDS who were already receiving treatment with celiprolol and exhibited normotension at baseline (119/71 mm Hg) demonstrated a notable decrease in BP (≈ −8/−5 mm Hg at 6 months). Nevertheless, no link was identified between this BP reduction and the incidence of symptomatic or asymptomatic arterial events. Therefore, in addition to its BP-lowering effect, alternative mechanisms may be responsible for the notable beneficial outcome observed in the ARCADE trial with irbesartan. Among the mechanisms proposed is the reduction in transforming growth factor–β signaling, which has been demonstrated to occur as a result of ARB treatment.[18] This is supported by evidence from a *col3a1* mutant mouse model of VEDS, in which stimulation of the transforming growth factor–β pathway was observed in aortic tissue.[19] Furthermore, the relative specificity of the benefit of losartan is indicated by our previous comparison of several antihypertensive agents in a mouse model[12]; for example, amlodipine was observed to decrease BP, yet simultaneously result in a deterioration of the aortic outcome.[12,19]

Irbesartan not only has a well-known safety profile, but is also available as a low-cost generic drug, both highly valuated advantages in the treatment of a rare disease. In patients with VEDS with normal to low BP at baseline while receiving celiprolol, the addition of irbesartan resulted in systolic BP levels <100 mm Hg in 9 of 29 patients (31.0%) at various visits over 2 years and in symptomatic hypotension in 4 patients (13.8%). Irbesartan had to be reduced in 4 of them (3 symptomatic

Table 3. Number and Localization of New Arterial Lesions at 1 Year and 2 Years

	Irbesartan (n=29)		Placebo (n=28)	
Treatment group	1 y*	2 y†	1 y‡	2 y§
Total	5	9	15	29
New lesion	2	5	11	20
Progression of preexisting lesion	3	4	4	9
Localization				
Cervical arteries	3	4	4	5
Thoracic and abdominal aortae	1	1	0	0
Abdominal visceral arteries	0	3	6	13
Iliofemoral arteries	1	1	3	8
Distal arteries (femoral, scapular)	0	0	2	3

Values are number of new arterial lesions detected by computed tomography angiography (CTA).

*No missing CTA at 1 year in the irbesartan group and 1 missing in the placebo group.

†Two missing CTAs at 2 years in the irbesartan group and 1 missing in the placebo group.

‡At 1 year, the total number of lesions (new lesion or progression of a preexisting lesion) was n=5/29 in the irbesartan group and n=15/28 in the placebo group (relative risk, 0.32 [95% CI, 0.10, 0.83]).

§At 2 years, the total number of lesions (new lesion or progression of a preexisting lesion) was n=9/29 in the irbesartan group and n=29/28 in the placebo group (relative risk, 0.30 [95% CI, 0.13, 0.61]).

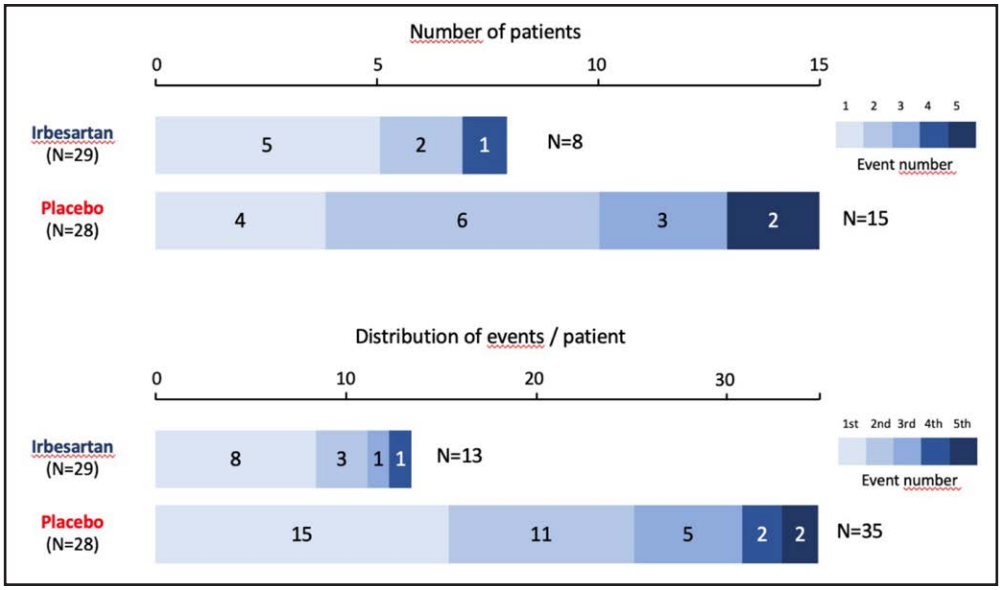

Figure 3. Distribution of primary composite end points at 2 years.
Top, Distribution of patients with primary composite outcomes in the 2 groups (irbesartan: 5, 2, or 1 patients with 1, 2, or 4 events, respectively; placebo: 4, 6, 3, or 2 patients with 1, 2, 3, or 5 events, respectively). **Bottom**, Distribution of first and subsequent primary composite outcomes in the 2 groups (irbesartan: 8 patients with a first event, 3 with a second event, and 1 each with a third or fourth event; placebo: 15 patients with a first event, 11 with a second event, 5 with a third event, and 2 each with a fourth or fifth event).

and one asymptomatic low BP) without drug withdrawal. Hypotension, whether symptomatic or not, was reported mainly in women (n=9/11). No other drug-related adverse events were observed. In our knock-in *col3a1* mutant mouse model, losartan reduced systolic BP more than the other antihypertensive agents, suggesting a particular activation of the renin-angiotensin system[12] or a particular sensitivity of a type III collagen defective arterial wall to angiotensin II.[11]

Limitations

A first limitation of our study is a smaller sample size (61 patients) than originally planned (108 patients) because of difficulties in recruiting patients with this rare disease who are not already treated with other cardiovascular drugs except celiprolol. Despite this limitation, the Kaplan-Meier event-free survival curve showed that the incidence of the primary composite outcome was significantly lower in the irbesartan group, taking into account the later onset of the fewer symptomatic arterial events compared with placebo. In addition, the existence of a significant beneficial effect of irbesartan is consistent with Poisson regression analysis taking into account the recurrence of events in the same patient. The differences between the placebo and irbesartan groups were consistent for both symptomatic and asymptomatic arterial events and for all arterial sites.

A second limitation comes from the use of irbesartan in combination with background celiprolol treatment in our trial for ethical reasons, as this is considered the reference treatment for patients with VEDS in France. Because the 2 drugs act on different receptors, they may act independently or partially synergistically, not only by achieving lower and more stable BP,[20] but also by interacting with the transforming growth factor–β signaling pathway,[18,21] involved in the aortic aneurysms pathogenesis.[22] Therefore, no conclusions can be drawn about the beneficial effects of irbesartan alone on the basis of our results. Another limitation is the lack of availability of celiprolol in other countries, particularly the United States, which limits the broad applicability of the study results. It would be reasonable to hypothesize that the observed effect of the irbesartan–celiprolol combination could be extended to other ARB–beta-blocker combinations. However, this requires further investigation, particularly given the unique properties of celiprolol.[20]

The third limitation is the external applicability of our findings. The patients enrolled closely match the clinical and genetic profiles described in larger cohorts,[3–5,7] suggesting that the results of the ARCADE trial can be extrapolated to the broader adult VEDS population. The reduced risk of the primary outcome was consistent across the predefined subgroups. Our investigation revealed no discernible interaction with age in this middle-aged group of patients, nor any effect associated with familial genetic status (index cases versus relatives). Although a trend toward a more significant reduction of composite events was noted in male patients (odds ratio, 0.5 [0.05, 1.22]), the small sample size (total of 21 men) precludes formal conclusions. A strong genotype–phenotype relationship has been described in patients with VEDS, with variants (mainly missense glycine and

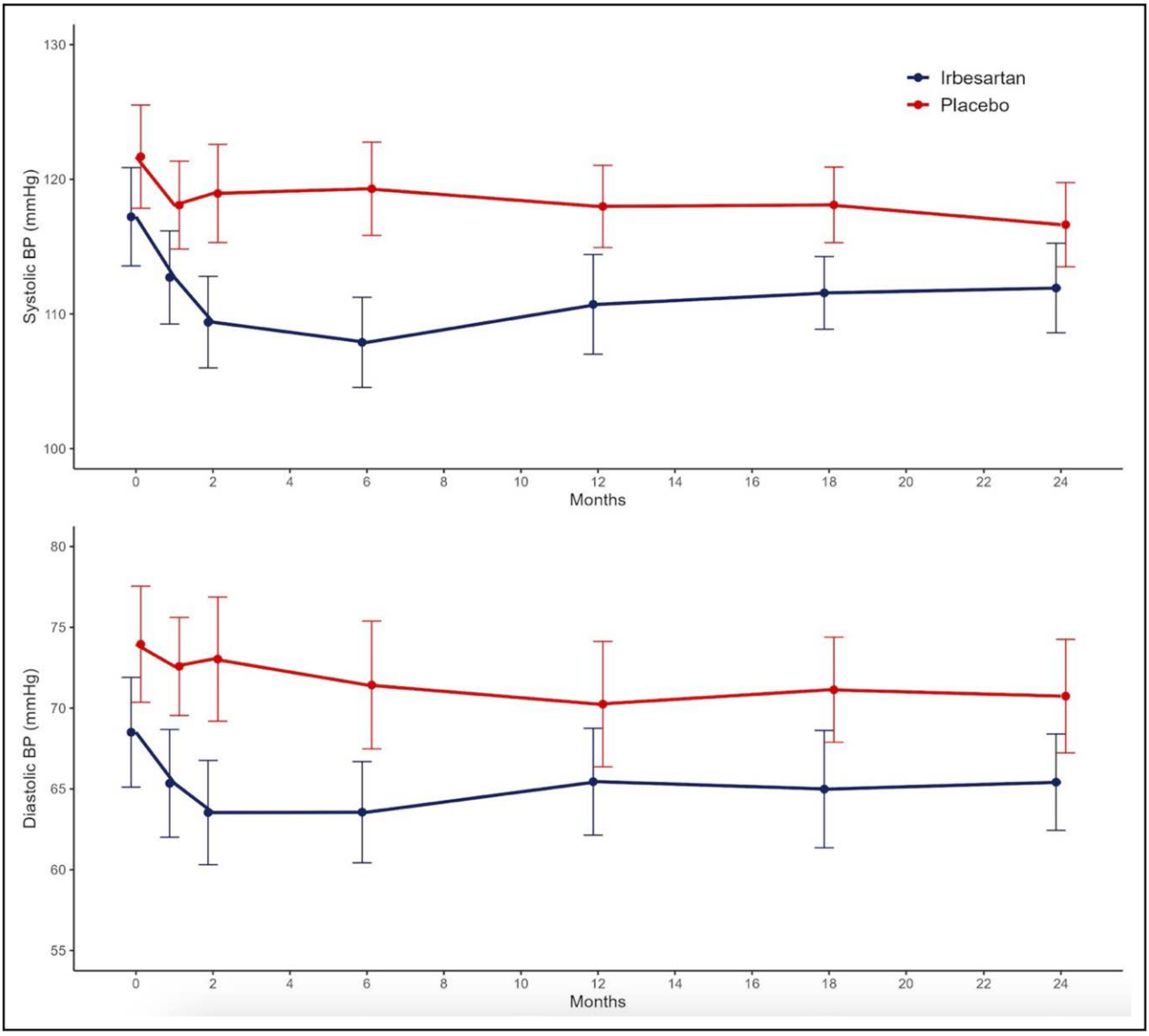

Figure 4. Time course evolution of systolic and diastolic blood pressure with irbesartan or placebo in patients with vascular Ehlers-Danlos syndrome during the 2-year study.

Dots and bars represent mean±1 SD. Time 0: randomization; time 1 to 24: months after randomization. The mean overall systolic blood pressure (BP; mixed model with adjustment on the initial BP value) was 111.7 (110.1, 113.4) vs 117.1 (115.4, 118.8) in the irbesartan and placebo groups, respectively (mean difference, −5.4 [−7.8, −3.0]; $P<0.001$). The mean overall diastolic BP (mixed model with adjustment on the initial BP value) was 66.0 (64.1, 67.9) vs 70.1 (68.2, 72.1) in the irbesartan and placebo groups, respectively (mean difference, −4.1453 [−6.9413, −1.3493]; $P=0.004$).

splicing in-phase) resulting in a dominant-negative effect leading to a more severe and earlier pathological condition than that observed in case of variants leading to haploinsufficiency.[4,23,24] The distribution of dominant-negative and haploinsufficiency variants in our study aligns with the 10% proportions observed in larger cohorts. When the statistical analysis was restricted to patients with DN–*COL3A1* variants (n=49/57), the reduction of events between active treatment and placebo was similar to that of the entire study, with the low number of haploinsufficiency–*COL3A1*–related patients with VEDS precluding a robust estimation of any differential effect.

Conclusions

In the current study, compared with placebo, irbesartan was associated with a lower risk of the composite outcome of severe symptomatic and asymptomatic arterial events over 2 years in adult patients with VEDS receiving celiprolol as background treatment. Therefore, unless contraindicated, the systematic use of an ARB such as

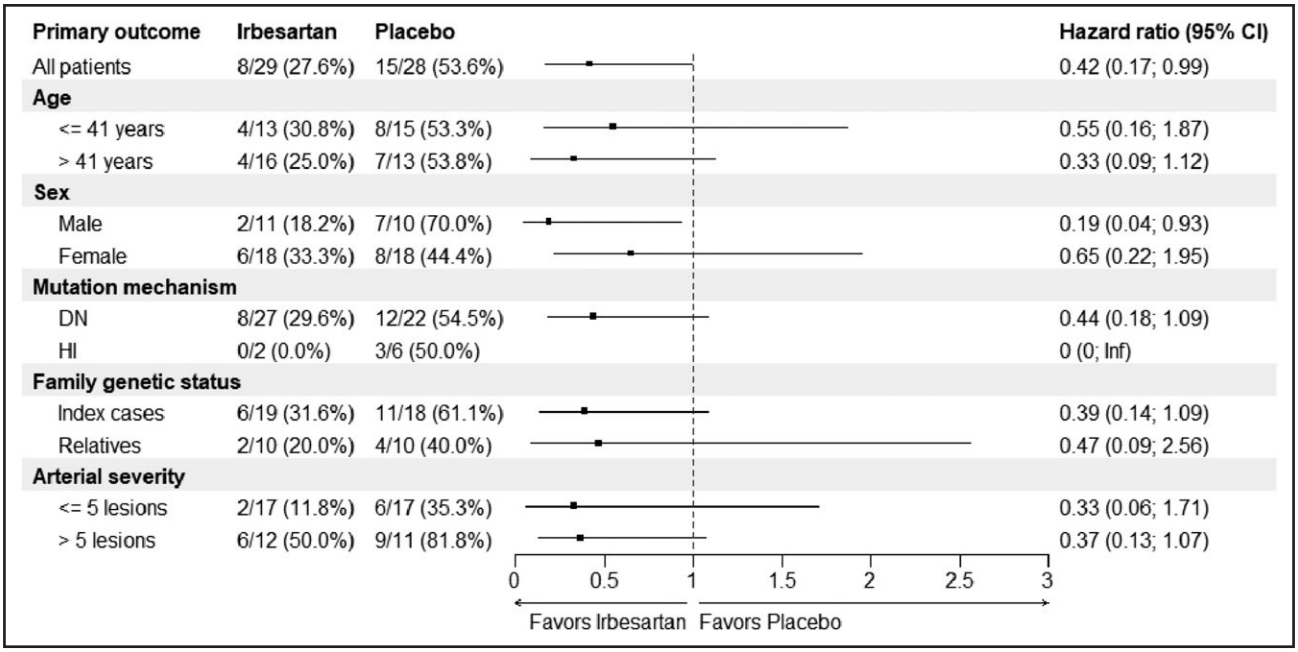

Figure 5. Forest plots for Cox proportional hazards models on the occurrence of primary composite outcomes over the 2-year study according to different subgroups.
DN indicates dominant negative; and HI, haploinsufficiency.

irbesartan is recommended in the medical therapeutic management of this rare life-threatening condition.

ARTICLE INFORMATION

Received October 23, 2024; accepted January 6, 2025.

Affiliations

PARCC (X.J., E.M., P.B., T.M., G.C.) and CIC1418 (M.A.), Institut National de la Santé et de la Recherche Médicale (INSERM), Université Paris Cité, France. Service de Médecine Génomique des Maladies Rares et DMU BioPhyGen (X.J., C. Billon, M.B.Y.), Service de Radiologie Vasculaire (E.M., F.P.), Service de Médecine Vasculaire et Centre de Référence des Maladies Artérielles Rares (M.F., S.A., M.E.H., N.D., T.M.), Unité de Recherche Clinique (E.L., G.C.), Service de Pharmacologie (P.B.), and Hypertension Department and DMU CARTE (M.A.), AP-HP, Hôpital Européen Georges-Pompidou, Paris, France. Service de Médecine Vasculaire, Hôpital Saint-Eloi, CHU Montpellier, France (S.A.). Service de Médecine Vasculaire, CHU de Toulouse, Hôpital Rangueil, Toulouse, France (A.B.-R., F.-X.L.). Unité Mixte de Recherche 1295 INSERM, Centre d'Epidémiologie et de Recherche en Santé des Populations, Toulouse III-Paul Sabatier University, Toulouse, France (A.B.-R., F.-X.L.). Departement de Médecine Vasculaire, CHU Caen Normandie, Caen, France (C.L.H.). Service de Médecine Vasculaire, CHU St-Etienne, Hôpital Nord, St-Etienne, France (C.L.H.). INSERM, U1059, Université Jean Monnet, St-Etienne, France (C.L.H.). INSERM, COMETE, GIP Cyceron, Université de Caen Normandie, Caen, France (D.L.). Service de Médecine Vasculaire, CHU Grenoble Alpes, Grenoble, France (C.S.). Service de Génétique Médicale, CHU Grenoble, Université Grenoble Alpes, INSERM 1209, Institut pour l'Avancée des Biosciences, Grenoble University Hospital, France (K.D.). Unité Médico Chirurgicale Vasculaire, Service de Médecine Interne, Hôpital Claude Huriez, CHRU Lille, France (M.L.). National HHT Reference Center and Genetics Department, Hospices Civils de Lyon, Femme-Mère-Enfants Hospital, Bron, France (S.D.-G.). INSERM, Biosanté Unit U1292, Université Grenoble Alpes, CEA, Grenoble, France (S.D.-G., P.H.). CHRU Nancy, Service de Médecine Vasculaire, Centre de Référence pour les Maladies Auto-immunes et Auto-inflammatoires, Centre de Compétence pour les Maladies Vasculaires Rares, Hôpitaux de Brabois, Vandoeuvre-lès-Nancy, France (S.Z.). INSERM, U1116, Défaillance Cardiovasculaire Aiguë et Chronique, Université de Lorraine, Nancy, France (S.Z.). AP-HM, CHU La Timone, Centre de Référence Pour le Syndrome de Marfan et Apparentés, Centre Aorte Timone, Université Aix-Marseille, Marseille, France (L.B.-T.). Hôpital Saint-André, CHU Bordeaux, France (C. Boulon). Dipartimento Medicina Molecolare, University La Sapienza, Italy (M.E.H.).

Acknowledgments

This study was funded by the French Ministry of Health (grant PHRC-N-2014-0387). The French Reference Centre for Rare Arterial Diseases (Drs Jeunemaitre, Frank, and Mirault) is part of the FAVAMULTI Network, both supported by the French Ministry of Health. The majority of the patients enrolled in ARCADE are also part of a French national prospective cohort (RaDiCoSEDVasc) 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-IO-COHO-03-01). The authors thank the patients and their families for their contributions to the authors' clinical research programs, which are also supported by grants from the Association DAVID and the Association Française pour les Syndromes d'Ehlers-Danlos.

Sources of Funding

The French Ministry of Health funded the trial through the Programme Hospitalier de Recherche Clinique (PHRC-N-2014-038). The funder had no role in data collection, analysis, or interpretation, writing of the manuscript, or the decision to submit for publication. The Clinical Investigation Centre (CIC1418), funded by INSERM and Assistance Publique–Hôpitaux de Paris, provided local support at the Paris Centre. The French Reference Centre for Rare Arterial Diseases, part of the FAVAMULTI Network, both of which are supported by the French Ministry of Health, provided support for the recruitment of patients. The Unité de Recherche Clinique at the Hôpital Européen Georges Pompidou, headed by Juliette Djadji-Prat, coordinated the entire protocol and study.

Disclosures

None.

Supplemental Material

Expanded Methods
Tables S1–S11
Figures S1–S5

REFERENCES

1. Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, et al. The 2017 international

classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175:8–26. Doi: 10.1002/ajmg.c.31552
2. 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;342:673–680. Doi: 10.1056/NEJM200003093421001
3. Frank M, Adham S, Seigle S, Legrand A, Mirault T, Henneton P, Albuisson J, Denarie N, Mazzella JM, Mousseaux E, et al. Vascular Ehlers-Danlos syndrome: long-term observational study. *J Am Coll Cardiol*. 2019;73:1948–1957. Doi: 10.1016/j.jacc.2019.01.058
4. Bowen JM, Hernandez M, Johnson DS, Green C, Kammin T, Baker D, Keigwin S, Makino S, Taylor N, Watson O, et al. Diagnosis and management of vascular Ehlers-Danlos syndrome: experience of the UK national diagnostic service, Sheffield. *Eur J Hum Genet*. 2023;31:749–760. Doi: 10.1038/s41431-023-01343-7
5. Demirdas S, van den Bersselaar LM, Lechner R, Bos J, Alsters SIM, Baars MJH, Baas AF, Baysal O, van der Crabben SN, Dulfer E, et al. Vascular Ehlers-Danlos syndrome: a comprehensive natural history study in a Dutch national cohort of 142 patients. *Circ Genom Precis Med*. 2024;17:e003978. Doi: 10.1161/CIRCGEN.122.003978
6. Buso G, Paini A, Agabiti-Rosei C, De Ciuceis C, Bertacchini F, Stassaldi D, Salvetti M, Ritelli M, Venturini M, Colombi M, et al. Despite celiprolol therapy, patients with vascular Ehlers-Danlos syndrome remain at risk of vascular events: a 12-year experience in an Italian referral center. *Vasc Med*. 2023;29:265–273. Doi: 10.1177/1358863x231215330
7. Shalhub S, Byers PH, Hicks KL, Coleman DM, Davis FM, De Caridi G, Weaver KN, Miller EM, Schermerhorn ML, Shean K, et al. A multi-institutional experience in vascular Ehlers-Danlos syndrome diagnosis. *J Vasc Surg*. 2020;71:149–157. Doi: 10.1016/j.jvs.2019.04.487
8. Ong K-T, Perdu J, De Backer J, Bozec E, Collignon P, Emmerich J, Fauret A-L, Fiessinger J-N, Germain DP, Georgesco G, et al. Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective andomized, open, blinded-endpoints trial. *Lancet*. 2010;376:1476–1484. Doi: 10.1016/S0140-6736(10)60960-9
9. Baderkhan H, Wanhainen A, Stenborg A, Stattin E-L, Björck M. Celiprolol treatment in patients with vascular Ehlers-Danlos syndrome. *Eur J Vasc Endovasc Surg*. 2021;61:326–331. Doi: 10.1016/j.ejvs.2020.10.020
10. Chu LC, Johnson PT, Dietz HC, Brooke BS, Arnaoutakis GJ, Black JH, Fishman EK. Vascular complications of Ehlers-Danlos syndrome: CT findings. *AJR Am J Roentgenol*. 2012;198:482–487. Doi: 10.2214/AJR.11.6603
11. Faugeroux J, Nematalla H, Li W, Clement M, Robidel E, Frank M, Curis E, Ait-Oufella H, Caligiuri G, Nicoletti A, et al. Angiotensin II promotes thoracic aortic dissections and ruptures in *Col3a1* haploinsufficient mice. *Hypertension*. 2013;62:203–208. Doi: 10.1161/HYPERTENSIONAHA.111.00974
12. Legrand A, Guery C, Faugeroux J, Fontaine E, Beugnon C, Gianfermi A, Loisel-Ferreira I, Verpont M-C, Adham S, Mirault T, et al. Comparative therapeutic strategies for preventing aortic rupture in a mouse model of vascular Ehlers-Danlos syndrome. *PloS Genet*. 2022;18:e1010059. Doi: 10.1371/journal.pgen.1010059
13. Pitcher A, Spata E, Emberson J, Davies K, Halls H, Holland L, Wilson K, Reith C, Child AH, Clayton T, et al; Marfan Treatment Trialists' Collaboration. Angiotensin receptor blockers and β blockers in Marfan syndrome: an individual patient data meta-analysis of andomized trials. *Lancet*. 2022;400:822–831. Doi: 10.1016/S0140-6736(22)01534-3
14. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145:247–254. Doi: 10.7326/0003-4819-145-4-200608150-00004
15. Isselbacher EM, Preventza O, Hamilton Black J, Augoustides JG, Beck AW, Bolen MA, Braverman AC, Bray BE, Brown-Zimmerman MM, Chen EP, et al; Peer Review Committee Members. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology joint committee on clinical practice guidelines. *Circulation*. 2022;146:e334–e482. Doi: 10.1161/CIR.0000000000001106
16. Boutouyrie P, Germain DP, Fiessinger J-N, Laloux B, Perdu J, Laurent S. Increased carotid wall stress in vascular Ehlers-Danlos syndrome. *Circulation*. 2004;109:1530–1535. Doi: 10.1161/01.CIR.0000121741.50315.C2
17. Mirault T, Pernot M, Frank M, Couade M, Niarra R, Azizi M, Emmerich J, Jeunemaître X, Fink M, Tanter M, et al. Carotid stiffness change over the cardiac cycle by ultrafast ultrasound imaging in healthy volunteers and vascular Ehlers-Danlos syndrome. *J Hypertens*. 2015;33:1890–1896. Doi: 10.1097/HJH.0000000000000617
18. Van Dorst DCH, De Wagenaar NP, Van Der Pluijm I, Roos-Hesselink JW, Essers J, Danser AHJ. Transforming growth factor-β and the renin-angiotensin system in syndromic thoracic aortic aneurysms: implications for treatment. *Cardiovasc Drugs Ther*. 2021;35:1233–1252. Doi: 10.1007/s10557-020-07116-4
19. Bowen CJ, Calderon Giadrosic JF, Burger Z, Rykiel G, Davis EC, Helmers MR, Benke K, Gallo MacFarlane E, Dietz HC. Targetable cellular signaling events mediate vascular pathology in vascular Ehlers-Danlos syndrome. *J Clin Invest*. 2020;130:686–698. Doi: 10.1172/JCI130730
20. 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;26:32–38. Doi: 10.1002/j.1552-4604.1986.tb02899.x
21. 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;147:412–421. Doi: 10.1038/sj.bjp.0706625
22. Dietz HC. TGF-beta in the pathogenesis and prevention of disease: a matter of aneurysmic proportions. *J Clin Invest*. 2010;120:403–407. Doi: 10.1172/JCI42014
23. Pepin MG, Schwarze U, Rice KM, Liu M, Leistritz D, Byers PH. Survival is affected by mutation type and molecular mechanism in vascular Ehlers-Danlos syndrome (EDS type IV). *Genet Med*. 2014;16:881–888. Doi: 10.1038/gim.2014.72
24. Frank M, Albuisson J, Ranque B, Golmard L, Mazzella JM, Bal-Theoleyre L, Fauret AL, Mirault T, Denarie N, Mousseaux E, et al. The type of variants at the COL3A1 gene associates with the phenotype and severity of vascular Ehlers-Danlos syndrome. *Eur J Hum Genet*. 2015;23:1657–1664. Doi: 10.1038/ejhg.2015.32