OPEN

Celiprolol

A Unique Selective Adrenoceptor Modulator

James J. Nawarskas, PharmD, Angela Cheng-Lai, PharmD, BCPS,† and William H. Frishman, MD‡*

Abstract: Celiprolol is a β-blocker with a unique pharmacologic profile: it is a β1-andrenoceptor antagonist with partial β2 agonist activity. Given this combination of effects, celiprolol may be better described as a selective adrenoreceptor modulator. It has antihypertensive and antianginal properties and is indicated for those uses in various countries around the world. In the United States, however, the proposed indication for this drug will be for the treatment of vascular type Ehlers–Danlos syndrome, a rare connective tissue disorder characterized by fragile arterial structure and an increased risk of life-threatening vascular complications. By reducing heart rate and pulsatile pressure, celiprolol may reduce the mechanical stress on collagen fibers within the arterial wall and be of benefit in patients with vascular type Ehlers–Danlos syndrome. The largest investigation of celiprolol in vascular Ehlers–Danlos syndrome was prematurely terminated due to significant benefit with celiprolol in reducing arterial events in patients with this condition. Celiprolol, therefore, represents a β-blocker that is unique from others in its class in both its pharmacology and clinical applications.

Key Words: celiprolol, Ehlers–Danlos, β-blockers, vascular Ehlers–Danlos syndrome, Ehlers–Danlos syndrome, Ehlers–Danlos syndrome type IV

(*Cardiology in Review* 2017;25: 247–253)

β-Adrenoceptor–blocking agents (also known as β1-adrenoceptor antagonists or β-blockers) are used to treat a variety of disorders such as arterial hypertension, systemic hypertension, angina, coronary heart disease, arrhythmias, hypertrophic cardiomyopathy, mitral valve prolapse, migraine, and glaucoma.[1–3] The pharmacological classification of these agents is based on their affinity, β1-selectivity, partial agonist activity, effects on other adrenergic receptors, and physicochemical properties.[1] For some conditions, the efficacy of the various β1-adrenoceptor antagonists is similar, whereas in other conditions, only certain subgroups have demonstrated therapeutic benefits. In the United States, there are currently 17 β-adrenoceptor antagonists available for the treatment of cardiovascular and other disorders, although globally there are over 30 available for clinical use (Figure 1).[4] Celiprolol (3-[3-acetyl-4-(3-t-butylamino-2-hydroxypropoxy)phenyl]-2,1-diethylurea hydrochloride; Figure 2) was developed as a third-generation β1-adrenoceptor antagonist with partial β2 agonist activity and a unique pharmacological profile.[5] Like β blockers, it demonstrates antihypertensive and antianginal activity; however, it lacks the typical side effects of the class, such as bronchoconstriction, depression of left ventricular function, and peripheral vasoconstriction.[5] This is likely a result of its β2 agonist activity.[2,6–9] Given this unique combination of pharmacologic effects, celiprolol is perhaps more accurately described as a selective adrenoceptor modulator (SAM). Furthermore, celiprolol's ability to stimulate β2-receptors, influence vascular tone, and directly affect smooth muscle suggests its potential usefulness in patients with cardiovascular disease and concomitant lung disease.[2,3,8] Recently, the unique properties of celiprolol have inspired investigation into its use in a rare connective tissue disorder—Ehlers–Danlos syndrome, vascular type (vEDS; formerly known as EDS type IV).

There are 6 major types of EDS, each defined according to signs and symptoms and thought to involve a unique connective tissue defect (Table 1).[10,11] vEDS is an autosomal dominant inherited connective tissue disorder (100% phenotypic penetrance) caused by structural defects of the pro α1 (III) chain of collagen type III (*COL3A1*) gene.[12,13] Mutations in the *COL3A1* gene result in decreased thermal stability and proteolytic processing irregularities, which subsequently lead to procollagen degradation.[13] Complications of vEDS include life-threatening arterial dissections and ruptures, vascular aneurysms, intestinal ruptures, and uterine ruptures.[14] The average life span of patients with vEDS is approximately 50 years of age, with manifestation of the disorder often evident by 20 years of age.[15,16] vEDS is suspected when a combination of clinical findings is present. The Villefranche criteria provide guidance on clinical diagnosis (Table 2).[14,17] The diagnosis is confirmed by the identification of a pathogenic mutation in *COL3A1* gene or the appearance of abnormal type III procollagen in cultured fibroblasts in patients with clinical features of vEDS.[15] Currently, there are no Food and Drug Administration (FDA)–approved therapies for vEDS.[18] Celiprolol was investigated for the treatment of vEDS because of the observed effects of reduced heart rate, mean, and pulsatile pressures in animals and in patients with hypertension and with potentially decreased continuous and pulsatile mechanical stress on collagen fibers within the arterial wall.[19] On the basis of these data and on the fragile connective tissues associated with vEDS, celiprolol was investigated as a preventive therapy for the life-threatening risks, specifically arterial dissections and ruptures and intestinal and uterine ruptures associated with vEDS.

PHARMACOKINETIC PROPERTIES OF CELIPROLOL

As a whole, β1-adrenoceptor antagonists have similar therapeutic effects; however, their pharmacokinetic properties differ.[19] This is attributed to the distinct aromatic ring structure of these compounds, which results in differences in absorption, metabolism, first-pass hepatic metabolism, lipid solubility, protein binding, and renal clearance among the drugs. Specifically, configuration of the asymmetric β-carbon of the side chain determines activation or blockade effect.[20] Celiprolol's aromatic ring structure (benzene) is similar to other β1-adrenoceptor antagonists and is most closely related to acebutolol (Figure 2).[21,22]

Absorption

β1-Adrenoceptor antagonists are either considered lipophilic or hydrophilic. Celiprolol is a hydrophilic agent, freely soluble in

From the *College of Pharmacy, University of New Mexico, Albuquerque, NM; †Department of Clinical Pharmacy, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY; and ‡Department of Medicine, New York Medical College/Westchester Medical Center, Valhalla, NY.

Supported by Acer Therapeutics, Cambridge, MA.

Correspondence: James J. Nawarskas, PharmD, College of Pharmacy, University of New Mexico, 2502 Marble NE, Albuquerque, NM 87131. E-mail Jnawarskas@salud.unm.edu

ISSN: 1061-5377/17/2505-0247
DOI: 10.1097/CRD.0000000000000159

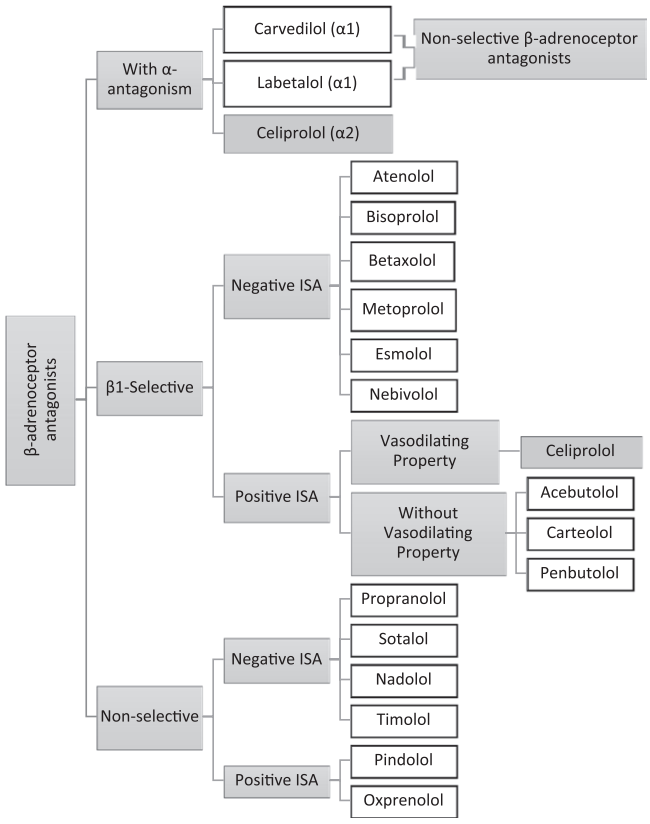

FIGURE 1. β-Adrenoceptor antagonists.[4] ISA indicates intrinsic sympathomimetic activity.

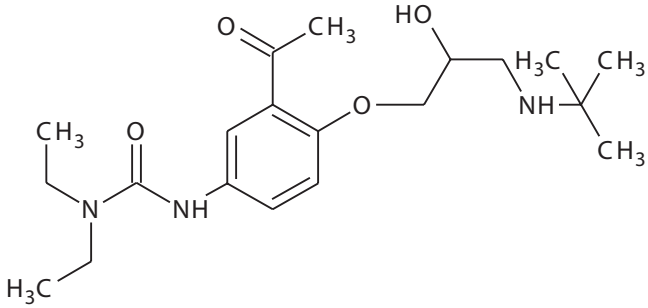

FIGURE 2. Celiprolol chemical structure.

water.[23] Most β1-adrenoceptor antagonists (except atenolol) are absorbed in the small intestine.[1] Mean peak plasma concentrations after oral doses of 100–600 mg of celiprolol range from 300 to 3000 μg/L.[23,24] The bioavailability of celiprolol is dose-dependent: 30% at 100 mg and 70% over the range 300–400 mg.[24,25] Food may impair this bioavailability; however, the effect is not clinically relevant with long-term therapy.[23] Grapefruit juice and orange juice, both inhibitors of the organic anion–transporting polypeptide 1A2 (OATP1A2), have been shown to cause a significant decrease in the oral absorption of celiprolol.[26] Although the clinical relevance of this interaction has not been fully assessed, studies have suggested that the effects of celiprolol on blood pressure and heart rate are not affected. Nevertheless, the marked reduction in celiprolol bioavailability in the presence of grapefruit or orange juice suggests that this interaction may be of clinical significance in some patients.[26,27] In addition, concomitant administration of drugs such as chlorthalidone, hydrochlorothiazide, theophylline, or digoxin may have an effect on its bioavailability.[23] As a class, β1-adrenoceptor antagonists are known to interact with several drugs, particularly with agents that affect cardiovascular function. A list of select drug interactions with celiprolol is found in Table 3.[2,25–28]

Distribution

Distribution of β1-adrenoceptor antagonists occurs rapidly from the blood to other tissues.[29] The distribution of celiprolol has been studied in animals and humans. Celiprolol was found to be a water-soluble substance that is widely distributed in all tissues, with the exception of the brain, after absorption.[24] This is likely due to its hydrophilic properties.[23,25,29] In vitro studies indicate that the rate of diffusion across the human placenta is 3–4 times lower than that of comparative β-blockers (propranolol, timolol, and labetalol) with approximately 25% plasma protein binding (Table 4).[24] It is unclear whether this translates to a lower risk of fetal complications with celiprolol.

Metabolism

Celiprolol is minimally metabolized, with only a very low percentage of a dose being excreted.[8] Similar to other β1-adrenoceptor antagonists, celiprolol displays first-pass metabolism. However, the concentration of celiprolol is greatly reduced before it reaches the systemic circulation. A small study in healthy volunteers demonstrated no drug accumulation with chronic dosing over a 7-day period.[8]

Excretion

According to their pharmacokinetic properties, β1-adrenoceptor drugs are divided into 2 categories: those eliminated via hepatic metabolism and those eliminated (unchanged) via the kidney.[30] The pharmacokinetics of celiprolol have been studied in animals and patients with primary hypertension and chronic stable angina pectoris.[24] Investigations have found that celiprolol is minimally metabolized and excreted unchanged via the urine and feces, with a half-life of approximately 4–5 hours (10–15% observed dose excreted in the urine).[23,24] One study also reports the possible urinary excretion of a celiprolol metabolite.[7]

A summary of celiprolol's pharmacokinetic properties is found in Table 4.[8,23]

PHARMACODYNAMIC PROPERTIES OF CELIPROLOL

Celiprolol was developed as a third-generation β-adrenoceptor antagonist with selective β1-antagonist, partial β2-agonist, and mild α2-antagonist actions. The α2 antagonism is weak and ineffective in blocking the effects of the α2 agonist clonidine. The α2 agonist effects of celiprolol are, therefore, believed to contribute little to its overall pharmacologic effect.[23] Its blockade of β1-adrenoreceptors reduces sympathoadrenal stimulation of the heart during physiological stress.[23] In addition, celiprolol's blockade of β1-adrenoreceptors reduces heart rate (negative chronotropic effect) in the sinoatrial node and decreases cardiac contractility (negative inotropic effect) in the myocardium.[23] Furthermore, studies indicate that celiprolol improves vasodilation through β2 agonism and may also act on β3 receptors as evidenced by a 2013 study of porcine coronary arteries, which demonstrated that celiprolol exerts β3-adrenoceptor agonistic activity with resulting vasorelaxation.[2,5,6] In addition, celiprolol may induce coronary vasodilation due to stimulation of the release of nitric oxide.[31] As a result of this activity profile, celiprolol may offer advantages over other β-adrenergic antagonists due to its bronchosparing properties, mild lipid effects, and minor cardiac conduction effects.[2]

TABLE 1. EDS Types

EDS Type	Distinguishing Characteristics	Estimated Frequency
Hypermobile	Chronic pain and joint hypermobility that may lead to subluxations and dislocations.	1 in 10,000 to 15,000 people
Classical	Skin hyperextensibility (stretchy) and joint hypermobility. Skin is smooth, velvety, and fragile.	1 in 20,000 to 40,000 people
Vascular	Most serious of all the EDS types due to possibility of arterial or organ rupture. Skin is usually thin and translucent, which is most apparent over the chest and abdomen.	1 in 90,000 to 250,000 people
Kyphoscoliosis	Joint laxity and weak muscle tone at birth with progressing scoliosis.	About 60 cases reported worldwide.
Arthrochalasia	Congenital hip dislocation often associated with severe generalized joint hypermobility with recurrent subluxations.	About 30 cases reported worldwide.
Dermatosparaxis	Severe skin fragility with substantial bruising. Skin is soft, doughy, and sagging.	About a dozen cases reported worldwide.

EDS indicates Ehlers–Danlos syndrome.
Data adapted from National Institutes of Health[10] and Ehlers Danlos Society.[11]

TABLE 2. vEDS Criteria

Major diagnostic criteria
- Arterial aneurysms, dissection, or rupture
- Intestinal rupture
- Uterine rupture during pregnancy
- Family history of vEDS

Minor diagnostic criteria
- Thin, translucent skin
- Characteristic facial appearance (thin vermilion of the lips, micrognathia, narrow nose, and prominent eyes)
- Acrogeria (an aged appearance to the extremities, particularly the hands)
- Carotid–cavernous sinus arteriovenous fistula
- Hypermobility of small joints
- Tendon/muscle rupture
- Early-onset varicose veins
- Pneumothorax/hemopneumothorax
- Easy bruising
- Chronic joint subluxations/dislocations
- Congenital dislocation of the hips
- Talipes equinovarus (clubfoot)
- Gingival recession

vEDS indicates vascular Ehlers–Danlos syndrome.
Data adapted from Byers and Holbrook,[12] Pepin et al,[15] and Oderich et al.[16]

TABLE 3. Celiprolol Drug Interactions

Agent	Nature of Interaction
Chlorthalidone and hydrochlorothiazide	Coadministration reduces the bioavailability of celiprolol
Nondihydropyridine calcium channel antagonists	In combination with β adrenergic antagonists, have additive effects on cardiac conductive system
Clonidine	β-Adrenergic antagonists may exacerbate the rebound hypertension, which can follow withdrawal of clonidine
Antidiabetic agents	In combination with β adrenergic antagonists, may intensify blood sugar–lowering effects of insulin and antidiabetic drugs and may mask symptoms of thyrotoxicosis or hypoglycemia
Nonsteroidal anti-inflammatory agents	May decrease the hypotensive effects of β-adrenergic antagonists
Orange juice	Reduces the bioavailability of celiprolol
Grapefruit juice	Reduces celiprolol plasma concentrations
Itraconazole	Almost doubles celiprolol plasma concentrations, likely due to increased absorption
Rifampin/rifampicin	Reduces celiprolol plasma concentrations, likely due to reduced absorption
Sympathomimetic agents	Counteract the effects of β-adrenergic antagonists
Concomitant use of other antihypertensive agents or tricyclic antidepressants, barbiturates, or phenothiazines	Potentiate the antihypertensive effects of β adrenergic antagonists

Data adapted from Riddell et al[25] and Lilja et al.[26–28]

Cardiovascular Effects

Studies support the idea that celiprolol reduces arteriolar resistance and improves blood flow without depressing cardiac function.[23] In healthy adults, a single 400-mg oral dose reduced standing diastolic blood pressure by approximately 10% with no change in systolic blood pressure.[32] In patients with hypertension, celiprolol moderated the positive chronotropic effects of sympathetic arousal, did not depress resting cardiac output, and reduced resting total peripheral resistance.[23] Regarding celiprolol's effect on cardiac conduction, in vivo animal studies demonstrated that treatment did not accelerate the ventricular rate during electrically induced atrial fibrillation despite stimulation of cardiac β2-adrenoceptors.[33] Furthermore, celiprolol had no membrane stabilizing or local anesthetic activity.[25,33] In a small study of patients with stable atrial fibrillation, the normalized maximum rate of left ventricular pressure reduction immediately after systole (dP/dt_{ip}) increased by 24%, and the left ventricular relaxation time constant declined by 20% after celiprolol administration.[23] In addition, Vyssoulis et al[34] found, in patients with left ventricular hypertrophy, that celiprolol lowered blood pressure to normal levels and reduced left ventricular size estimated from

TABLE 4. Pharmacokinetic Properties of Celiprolol

Absorption	30% After 100 mg; 74% After 400 mg
Plasma $T_{1/2}$	4–5 hours
C_{max}	300–3000 μg/L after oral doses of 100–600 mg
Metabolism	Minimal
Excretion	10–15% of oral dose excreted in urine, remainder in feces

Data adapted from Caruso et al[8] and Smith and Wolf.[24]

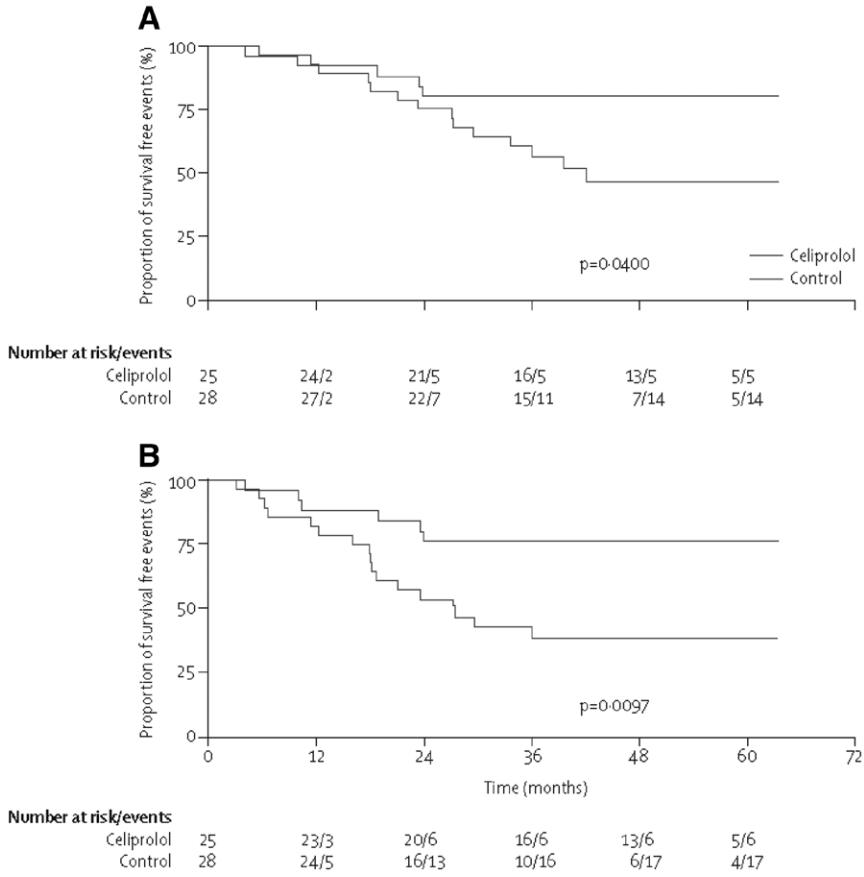

FIGURE 3. Kaplan–Meier curves of event-free survival in 53 patients with vascular Ehlers–Danlos syndrome. Primary end point (A). Primary and secondary endpoints (B). Reprinted with permission from the study by Ong et al.[43]

end-systolic and diastolic diameters, interventricular septal thickness, and posterior wall thickness at end diastole and end systole.

Small studies with celiprolol in patients with heart failure have shown variable results. In 1 study of 16 patients with reduced left ventricular ejection fraction (LVEF), 3 months of celiprolol therapy showed hemodynamic benefits and improved LVEF in patients with nonischemic cardiomyopathy, but the benefits in those with ischemic cardiomyopathy were mixed.[35] A larger study of 132 patients with reduced LVEF showed no difference between celiprolol and placebo in the primary end point of change in functional status (measured by the Goldman score) after 1 year of treatment.[36] Some of the secondary efficacy measures showed an advantage with celiprolol (heart rate was reduced more and DiBianco heart failure score, which is a composite of exertional and decubitus dyspnea, asthenia, and leg edema was reduced more), but other efficacy measures showed no significant differences compared to placebo (LVEF, end-diastolic diameter, fractional shortening, and exercise duration).[36] In aggregate, although these small trials did not show consistent efficacy with celiprolol for treating heart failure, they did suggest that the drug was safe in this population.

Respiratory Effects

The effects of celiprolol on the respiratory function of healthy patients and asthmatic patients have been studied.[36] Although respiratory function in patients with asthma was not changed with single doses of celiprolol (200 or 400 mg), bronchospasm and asthma have been reported in nonasthmatic patients with ischemic heart disease and hypertension being treated with celiprolol.[23,37,38] Monitoring for respiratory symptoms is, therefore, still recommended with the use of celiprolol in both asthmatic and nonasthmatic patients.[38]

Metabolic Effects

Similar to α-adrenoceptor antagonists, but unlike many other β1-adrenoceptor antagonists, celiprolol has no harmful effects on lipid and lipoprotein profiles but may have mild beneficial effects.[39] In a study of 100 patients with hypertension, celiprolol 200 mg once daily reduced low-density lipoprotein cholesterol (LDL-C) levels in hyperlipidemic patients (baseline LDL-C >160 mg/dL) by 16.9% and total cholesterol by 12.8%. No significant changes were observed in patients with baseline LDL-C levels lower than 160 mg/dL.[39]

In a small placebo-controlled, crossover study, celiprolol 100–400 mg once daily did not induce significant changes in glomerular filtration rate, renal plasma blood flow, plasma renin activity, filtration fraction, serum creatinine, aldosterone, or urinary enzymes.[40]

CLINICAL TRIALS

Four trials demonstrated the role of celiprolol in improving hypertension and vascular elasticity. In 1988, Donaldson et al[41] evaluated the hemodynamic effects of celiprolol in a small group (n = 10) of patients diagnosed with ischemic heart disease. Cardiac catheterization was performed, and left ventricular pressure and aortic pressure were recorded for 30 minutes post celiprolol treatment (intravenous infusion of 10 mg over 5 minutes). The measurements

were taken at rest, in sinus rhythm, and during atrial pacing at a rate of 100 bpm. Results of the study demonstrated that celiprolol exerted a vasodilatory effect without depressing cardiac function.[41]

A randomized, double-blind study was conducted in 2 centers over 9 months to understand the pathogenesis of the vascular lesions of vEDS. Ninety-eight patients with essential hypertension were treated with either 200-mg celiprolol or 10-mg enalapril.[19] The efficacy was similar in both groups and indicated that the decrease in carotid artery internal diameter was significantly related to the reduction in pulse pressure rather than mean blood pressure.[19]

Roman et al[42] utilized duplex echo Doppler techniques to determine the site of celiprolol's vasodilating effect. Thirty-five hypertensive patients were treated with increasing doses of celiprolol, 200 and 400 mg, over 15 days. Duplex echo Doppler was used to measure forearm (brachial artery) arterial and arteriolar vasodilation, before and during each celiprolol dose period. Celiprolol significantly ($P < 0.05$) increased brachial artery diameter and blood flow velocity compared to baseline. Statistically significant ($P < 0.05$) changes were also seen in forearm vascular measures: resistance decreased and compliance increased in response to celiprolol. These changes, except for blood flow velocity, occurred in a dose-dependent manner.[42]

These trials formed the backdrop for a study of celiprolol in vEDS, a condition in which reduction of arterial wall stress and increased vascular elasticity would likely be beneficial.

In 2010, Ong et al[43] demonstrated the reduction of arterial and organ complications in patients with vEDS after treatment with celiprolol. The Beta-Blockers in Ehlers-Danlos Syndrome (BBEST) study was a prospective, multicenter, randomized, open trial with blinded assessment of clinical events that evaluated 53 patients who received either celiprolol or no treatment over a planned 5 years. The inclusion/exclusion criteria for this study were adapted from the Villefranche diagnostic criteria as shown in Table 2.[43] Patients treated with celiprolol demonstrated a reduction in arterial events 3-fold greater than untreated patients (Figures 3 and 4).[43] These results were achieved without significant changes in heart rate or blood pressure; the reduction in events was statistically significantly different from controls in the subset of vEDS patients with *COL3A1* mutations.[43,44] In addition, celiprolol demonstrated mild vasodilating effects in the hypertensive vEDS patients.[42]

ADVERSE EFFECTS

Pooled data from clinical trials of patients with primary hypertension and/or angina pectoris reported no difference in adverse events between celiprolol and placebo (Figure 5).[3] Additional analyses have found celiprolol to not induce clinically significant bradycardia compared to propranolol and to produce less dizziness, fatigue, and tiredness compared to atenolol—signifying an advantageous tolerability profile.[23] Nonetheless, as with other

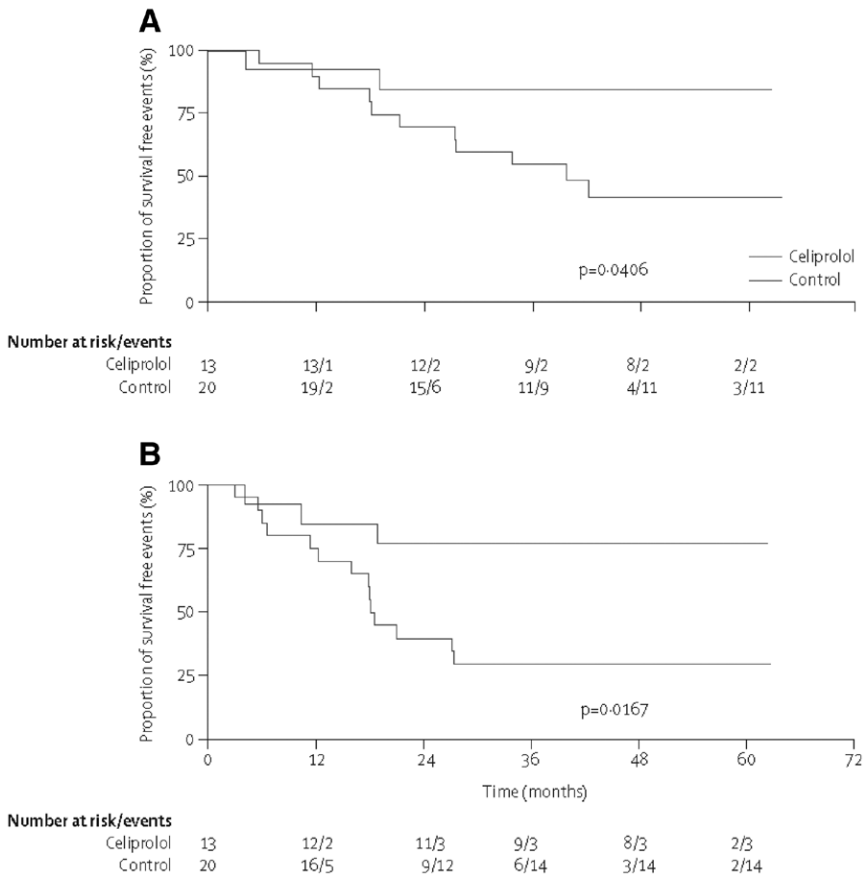

FIGURE 4. Kaplan–Meier curves of event-free survival in 33 patients with vascular Ehlers–Danlos syndrome with positive *COL3A1* mutation. Primary end point (A). Primary and secondary end points (B). Reprinted with permission from the study by Ong et al.[43]

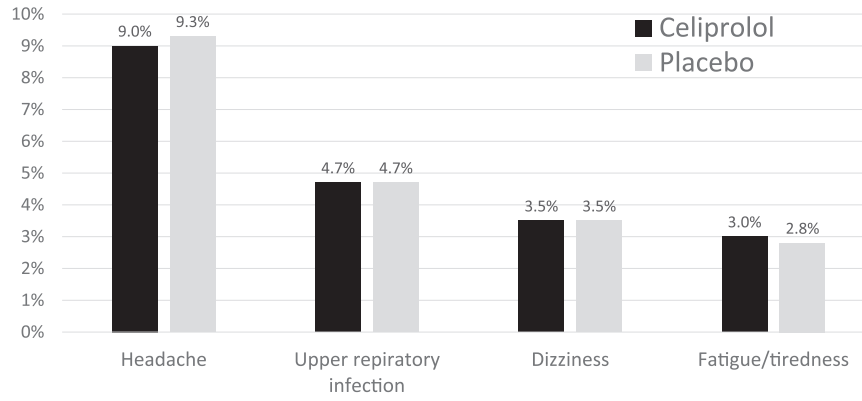

FIGURE 5. Most frequent adverse effects of celiprolol reported in double-blind, placebo-controlled trials (n = 2884). Reproduced with permission from the study by Lamon.[3]

β-blockers, celiprolol should not be used in patients with cardiogenic shock, decompensated heart failure, sick sinus syndrome, second- or third-degree heart block, or severe bradycardia.[45] Celiprolol, unlike other β-blockers, may relax bronchial smooth muscle, rendering it theoretically safe for use in patients with pulmonary disease.[45] In fact, several studies have shown celiprolol to not significantly affect respiratory function in patients with chronic obstructive lung disease[46,47] or asthma.[48,49] However, there have been reports of asthma and bronchospasm occurring in patients receiving celiprolol[23,38] and a case of hypersensitivity pneumonitis occurring with celiprolol, which recurred upon rechallenge of the drug.[50] Therefore, caution should still be exercised in patients with lung disease who are taking celiprolol, and monitoring for respiratory symptoms is still recommended even in patients without lung disease.[38]

USE IN VASCULAR EHLERS–DANLOS SYNDROME

Celiprolol is approved in many countries for the treatment of cardiovascular disorders; however, it is not yet approved in the United States for any indication. In 2015, the FDA granted celiprolol orphan drug status for the treatment of vEDS.[51]

Due to mutations in *COL3A1* and abnormal vascular smooth muscle cell signaling, patients with vEDS have high carotid wall stress (steady or pulsatile) and are at high risk for arterial dissection and rupture.[52] A reduction in the amplitude of carotid wall stress, along with the reduction of heart rate, and dP/dt have been suggested as potential benefits of celiprolol as preventive therapy for vEDS.[52] The clinical use of celiprolol as a preventative measure for the life-threatening arterial dissections and ruptures and organ ruptures associated with vEDS has been suggested based on the agent's capacity to reduce heart rate, mean pressure, and pulsatile pressure. Thus, celiprolol can decrease the continuous and pulsatile mechanical stress on collagen fibers within the arterial wall.[43,51] In addition, celiprolol is thought to strengthen the arterial wall potentially via the upregulation of collagen synthesis. Given the strong associations between β-adrenoceptors and transforming growth factor-β (TGFβ) pathways, Ong et al[43] suggested that β2 stimulation by celiprolol could enhance collagen synthesis via the TGFβ pathway. Moreover, Brooke[44] suggested that β-adrenoceptor blockers suppress TGFβ expression, which could result in decreased matrix turnover, which ultimately reduces the continuous mechanical stress on collagen fibers within the vascular wall and increases the elasticity of the radial artery.

CONCLUSIONS

In a recent publication, Thanawala et al[53] recommend against grouping all β-adrenoceptor antagonists into 1 class. The authors discussed a 3-state model of receptor activation that correlated with biased signaling of ligands. This was best represented when reviewing clinical data that demonstrated that not all β-adrenoceptor antagonists were effective in treating congestive heart failure.[53] This further confirms the idea that classification of β-adrenoceptor antagonists should be founded on several factors: affinity, β1-selectivity, partial agonist activity, and physicochemical properties.[1] On the basis of celiprolol's unique pharmacologic profile, a β1 adrenergic antagonist with partial β2 agonist activity, reported β3-agonism, mild α2-antagonism, lack of membrane-stabilizing or local anesthetic activity, vasodilator properties, and the minimal occurrence of typical side effects of the β-adrenergic antagonist class (eg, bronchoconstriction, depression of left ventricular function, and peripheral vasoconstriction), one may consider labeling celiprolol as a SAM rather than as a β-blocker. Moreover, in light of the associations reported between β-adrenergic receptors and the TGFβ signaling cascade, investigation into celiprolol's therapeutic efficacy via this mechanism is likely to further contribute to management of patients with vEDS and perhaps other rare cardiovascular diseases such as Loeys–Dietz syndrome and Marfan syndrome, in which TGFβ is believed to play a significant role in disease pathogenesis.[43,54]

vEDS is a rare genetic connective tissue disorder with life-threatening complications that include arterial dissections and ruptures, and intestinal and uterine ruptures.[14] Currently, there are no FDA-approved therapies for vEDS in the United States, and physicians face the challenge of establishing an effective preventative treatment plan for their patients.[18,55] Given its good tolerability and efficacy in a controlled, randomized clinical trial in preventing catastrophic vascular events and solid-organ ruptures, celiprolol may represent an agent with the ability to preemptively reduce the morbidity and mortality associated with vEDS. As such, it would represent a unique and innovative use of an agent from a class of drugs with a well-established track record of efficacy in treating other cardiovascular conditions.

REFERENCES

1. Borchard U. Pharmacological properties of β-adrenoceptor blocking drugs. *J Clin Bas Cardiol*. 1998;1:5–9.
2. Frishman WH. Clinical perspective on celiprolol: cardioprotective potential. *Am Heart J*. 1991;121(2 Pt 2):724–729.
3. Lamon KD. Clinical safety and efficacy of celiprolol. *Am Heart J*. 1991;121(2 Pt 2):683–687.

4. Frishman WH. Alpha- and beta-adrenergic blocking drugs. In: Frishman WH, Sica DA, eds. *Cardiovascular Pharmacotherapeutics. 3rd ed. Abridged and Updated*. Minneapolis, MN: Cardiotext Publishing; 2012;57–85.
5. Perrone MH, Barrett JA. Preclinical pharmacology of celiprolol: a cardioselective beta-adrenergic antagonist and mild vasodilator. *Am Heart J*. 1991;121(2 Pt 2):677–683.
6. Abdelkrim MA, Martignat L, Gogny M, et al. Celiprolol induces β(3)-adrenoceptors-dependent relaxation in isolated porcine coronary arteries. *Can J Physiol Pharmacol*. 2013;91:791–796.
7. Buskin JN, Upton RA, Sörgel F, et al. Specific and sensitive assay of celiprolol in blood, plasma and urine using high-performance liquid chromatography. *J Chromatogr*. 1982;230:454–460.
8. Caruso FS, Doshan HD, Hernandez PH, et al. Celiprolol: pharmacokinetics and duration of pharmacodynamic activity. *Br J Clin Pract Suppl*. 1985;40:12–16.
9. Louis WJ, Drummer OH, Tung LH. Pharmacology of celiprolol. *Cardiovasc Drugs Ther*. 1991;4(suppl 6):1281–1285.
10. National Institutes of Health, U.S. National Library of Medicine. Ehlers-Danlos Syndrome. Available at: https://ghr.nlm.nih.gov/condition/ehlers-danlos-syndrome. Accessed June 21, 2017.
11. Ehlers Danlos Society. EDS Types. Available at: https://ehlers-danlos.com/eds-types/. Accessed June 21, 2017.
12. Byers PH, Holbrook KA. Molecular basis of clinical heterogeneity in the Ehlers-Danlos syndrome. *Ann NY Acad Sci*. 1985;460:298–310.
13. Superti-Furga A, Gugler E, Gitzelmann R, et al. Ehlers-Danlos syndrome type IV: a multi-exon deletion in one of the two COL3A1 alleles affecting structure, stability, and processing of type III procollagen. *J Biol Chem*. 1988;263:6226–6232.
14. Beighton P, De Paepe A, Steinmann B, et al. Beighton P, De Paepe A, Steinmann B, et al. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet*. 1998;77:31–37.
15. Pepin M, Schwarze U, Superti-Furga A, et al. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med*. 2000;342:673–680.
16. Oderich GS, Panneton JM, Bower TC, 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.
17. Beridze N, Frishman WH. Vascular Ehlers-Danlos syndrome: pathophysiology, diagnosis, and prevention and treatment of its complications. *Cardiol Rev*. 2012;20:4–7.
18. Lum YW, Brooke BS, Black JH 3rd. Contemporary management of vascular Ehlers-Danlos syndrome. *Curr Opin Cardiol*. 2011;26:494–501.
19. Boutouyrie P, Bussy C, Hayoz D, et al. Local pulse pressure and regression of arterial wall hypertrophy during long-term antihypertensive treatment. *Circulation*. 2000;101:2601–2606.
20. Frishman W. Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 1. Pharmacodynamic and pharmacokinetic properties. *Am Heart J*. 1979;97:663–670.
21. PubChem National Institute for Health. Celiprolol Resources Page. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/celiprolol. Accessed April 5, 2017.
22. PubChem National Institute for Health. Acebutolol Resources Page. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/acebutolol. Accessed April 5, 2017.
23. Milne RJ, Buckley MM. Celiprolol. An updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in cardiovascular disease. *Drugs*. 1991;41:941–969.
24. Smith RD, Wolf PS. Celiprolol. *New Drugs Annu Cardiovasc Drugs*. 1984;2:19–35.
25. Riddell JG, Shanks RG, Brogden RN. Celiprolol. A preliminary review of its pharmacodynamic and pharmacokinetic properties and its therapeutic use in hypertension and angina pectoris. *Drugs*. 1987;34:438–458.
26. Lilja JJ, Backman JT, Laitila J, et al. Itraconazole increases but grapefruit juice greatly decreases plasma concentrations of celiprolol. *Clin Pharmacol Ther*. 2003;73:192–198.
27. Lilja JJ, Juntti-Patinen L, Neuvonen PJ. Orange juice substantially reduces the bioavailability of the beta-adrenergic-blocking agent celiprolol. *Clin Pharmacol Ther*. 2004;75:184–190.
28. Lilja JJ, Niemi M, Neuvonen PJ. Rifampicin reduces plasma concentrations of celiprolol. *Eur J Clin Pharmacol*. 2004;59:819–824.
29. Riddell JG, Harron DW, Shanks RG. Clinical pharmacokinetics of beta-adrenoceptor antagonists. An update. *Clin Pharmacokinet*. 1987;12:305–320.
30. Frishman WH. Beta-adrenoceptor antagonists: new drugs and new indications. *N Engl J Med*. 1981;305:500–506.
31. Asanuma H, Node K, Minamino T, et al. Celiprolol increases coronary blood flow and reduces severity of myocardial ischemia via nitric oxide release. *J Cardiovasc Pharmacol*. 2003;41:499–505.
32. Busst CM, Bush A. Comparison of the cardiovascular and pulmonary effects of oral celiprolol, propranolol and placebo in normal volunteers. *Br J Clin Pharmacol*. 1989;27:405–410.
33. Pruss TP. Celiprolol: its profile as a potential antiarrhythmic agent. *Am Heart J*. 1988;116(5 Pt 2):1412–1415.
34. Vyssoulis GP, Karpanou EA, Pitsavos CE, et al. Regression of left ventricular hypertrophy in systemic hypertension with beta blockers (propranolol, atenolol, metoprolol, pindolol and celiprolol). *Am J Cardiol*. 1992;70:1209–1211.
35. Hennersdorf MG, Perings C, Vester EG. Hemodynamic effects of celiprolol in patients with ischemic and non-ischemic cardiomyopathy. *Int J Cardiol*. 1999;68:289–295.
36. Witchitz S, Cohen-Solal A, Dartois N, et al. Treatment of heart failure with celiprolol, a cardioselective beta blocker with beta-2 agonist vasodilatory properties. The CELICARD Group. *Am J Cardiol*. 2000;85:1467–1471.
37. Bruschi C, Casali L, Cerveri I, et al. Effects of celiprolol on the bronchial reactivity in asthma. *Am J Cardiol*. 1988;61:53C–54C.
38. Ahmed R, Branley H. Reversible bronchospasm with the cardio-selective beta-blocker celiprolol in a non-asthmatic subject. *Respir Med CME*. 2009;2:141–143.
39. Vyssoulis GP, Karpanou EA, Pitsavos CE, et al. Differentiation of beta-blocker effects on serum lipids and apolipoproteins in hypertensive patients with normolipidaemic or dyslipidaemic profiles. *Eur Heart J*. 1992;13:1506–1513.
40. Lucarini AR, Salvetti A. Systemic and renal hemodynamic effects of celiprolol in essential hypertensives. *Am J Cardiol*. 1988;61:45C–48C.
41. Donaldson RM, Williams LA, Lee EH. Acute hemodynamic effects of celiprolol. *Am J Cardiol*. 1988;61:49C–51C.
42. Roman O, Meza N, Klenner C. Effect of celiprolol on large and small arteries of the forearm circulation in hypertensive patients. *Cardiovasc Drugs Ther*. 1990;4:745–749.
43. Ong KT, Perdu J, De Backer 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;376:1476–1484.
44. Brooke BS. Celiprolol therapy for vascular Ehlers-Danlos syndrome. *Lancet*. 2010;376:1443–1444.
45. Pruss TP, Khandwala A, Wolf PS, et al. Celiprolol: a new beta adrenoceptor antagonist with novel ancillary properties. *J Cardiovasc Pharmacol*. 1986;8(suppl 4):S29–S32.
46. Fogari R, Zoppi A, Tettamanti F, et al. Comparative effects of celiprolol, propranolol, oxprenolol, and atenolol on respiratory function in hypertensive patients with chronic obstructive lung disease. *Cardiovasc Drugs Ther*. 1990;4:1145–1149.
47. Chahuán M, Corradi L, Román O, et al. [Safety and efficacy of celiprolol in hypertensive patients with chronic obstructive lung disease]. *Rev Med Chil*. 2000;128:59–63.
48. Clauzel AM, Jean T, Etienne R, et al. Effect of long-term treatment with celiprolol on pulmonary function in a group of mild hypertensive asthmatics. *J Int Med Res*. 1988;16(suppl 1):27A–33A.
49. Szmidt M, Minc P, Wasiak W. [Comparison of the influence of celiprolol, metoprolol and atenolol on pulmonary ventilation in patients with asthma]. *Pneumonol Alergol Pol*. 1999;67:452–461.
50. Lombard JN, Bonnotte B, Maynadie M, et al. Celiprolol pneumonitis. *Eur Respir J*. 1993;6:588–591.
51. US Food and Drug Administration. Search Orphan Drug Designations and Approvals. Available at: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=456714. Accessed April 5, 2017.
52. Boutouyrie P, Germain DP, Fiessinger JN, et al. Increased carotid wall stress in vascular Ehlers-Danlos syndrome. *Circulation*. 2004;109:1530–1535.
53. Thanawala VJ, Forkuo GS, Stallaert W, et al. Ligand bias prevents class equality among beta-blockers. *Curr Opin Pharmacol*. 2014;16:50–57.
54. MacCarrick G, Black JH 3rd, Bowdin S, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med*. 2014;16:576–587.
55. De Paepe A, Malfait F. Bleeding and bruising in patients with Ehlers-Danlos syndrome and other collagen vascular disorders. *Br J Haematol*. 2004;127:491–500.