Hypertension

ORIGINAL ARTICLE

Aprocitentan for Blood Pressure Reduction in Black Patients

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BACKGROUND: Black individuals frequently present with resistant hypertension and disproportionately increased cardiovascular risk. We investigated the blood pressure (BP)-lowering effect of the dual endothelin receptor antagonist aprocitentan in Black individuals enrolled in the PRECISION study (Parallel-Group, Phase 3 Study with Aprocitentan in Subjects with Resistant Hypertension).

METHODS: Patients with confirmed resistant hypertension were randomized to aprocitentan 12.5 mg, 25 mg, or placebo for 4 weeks (part 1). They subsequently received aprocitentan 25 mg for 32 weeks (part 2) before re-randomization to aprocitentan 25 mg or placebo (part 3).

RESULTS: Eighty-two patients randomized in the PRECISION study were Black individuals. At week 4, aprocitentan 12.5 and 25 mg reduced office trough systolic BP (−11.3 and −11.9 mm Hg) to a similar degree as placebo (−12.0 mm Hg). Using 24-hour ambulatory BP monitoring, the placebo effect was minimal (−0.7 mm Hg), and aprocitentan reduced systolic BP by 4.0 and 8.6 mm Hg. During part 2, office BP continued to decrease (−16.4 mm Hg at week 36). In part 3, office and ambulatory systolic BP increased on placebo (+9.9 and +8.1 mm Hg, respectively), whereas the BP-lowering effect was maintained with aprocitentan. Aprocitentan markedly reduced albuminuria during the study. The most frequent adverse event was peripheral edema, occurring in 3 patients (10%) receiving aprocitentan 25 mg versus none receiving aprocitentan 12.5 mg or placebo.

CONCLUSIONS: Aprocitentan reduced BP and albuminuria in Black individuals with resistant hypertension. The BP-lowering efficacy was similar to that of the overall PRECISION population. Aprocitentan may represent an important addition to the often difficult-to-control hypertension in Black individuals. ***(Hypertension.* 2025;82:601–610. DOI: 10.1161/HYPERTENSIONAHA.124.24142.)** • **Supplement Material**.

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Hypertension affects ≈45% of the US adult population[1] and is a major risk factor for cardiovascular disease. For Black individuals, the prevalence is even higher, reaching 57%.[1] Hypertension in Black individuals is more difficult to treat[2,3] and is frequently a true resistant hypertension (RHT), defined as not adequately controlled blood pressure (BP) despite the concurrent use of at least 3 antihypertensive drugs from different classes, including a diuretic.[4] RHT carries an increased risk of major cardiovascular-renal events, including stroke, myocardial infarction, heart failure, and major loss of kidney function, beyond nonresistant forms.[5–9] Achieving lower BP in the Black population should play an important role in reducing disparities in hypertension-related outcomes.

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ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

This is the first study reporting on the efficacy of a dual endothelin receptor antagonist in the treatment of Black patients with confirmed resistant hypertension.

What Is Relevant?

Treatment with aprocitentan produced clinically meaningful and sustained blood pressure reductions in Black patients with resistant hypertension when added to a combination of 3 drugs that were unable to control blood pressure. Aprocitentan was safe and well tolerated, even in patients with chronic kidney disease.

Clinical/Pathophysiological Implications?

Achieving high rates of blood pressure control with aprocitentan in the Black population may have implications in the reduction of disparities in hypertension-related outcomes.

Nonstandard Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitoring
BP	blood pressure
CKD	chronic kidney disease
ET_A	endothelin A
ET_B	endothelin B
PRECISION	Parallel-Group, Phase 3 Study with Aprocitentan in Subjects with Resistant Hypertension
RHT	resistant hypertension
SBP	systolic blood pressure
UACR	urine albumin-to-creatinine ratio at baseline

Conventional antihypertensive strategies have not targeted endothelin, although endothelin is an important contributor to the pathogenesis of hypertension, especially RHT.[10,11] Hypertensive Black patients have higher plasma and vascular endothelin-1 concentrations than Whites,[12,13] and an increased prevalence of salt-sensitive and low-renin hypertension,[14,15] suggesting a critical role for endothelin. Endothelin-1 production is also increased in patients with other risk factors for RHT, such as obesity, diabetes, and chronic kidney disease (CKD),[11] all of which have a high prevalence in Black individuals. Evidence, therefore, suggests that Black individuals with RHT could particularly benefit from treatment with an endothelin receptor antagonist.

Aprocitentan is an oral dual $endothelin_A$/$endothelin_B$ (ET_A/ET_B) receptor antagonist with a long half-life of 44 hours.[16,17] In preclinical models of hypertension, especially low-renin models,[18] and in patients with hypertension, aprocitentan as monotherapy demonstrated a marked BP-lowering effect, numerically superior to that of lisinopril.[19] In the PRECISION study (Parallel-Group, Phase 3 Study with Aprocitentan in Subjects with Resistant Hypertension),[20] aprocitentan produced clinically relevant and sustained BP reductions over a 48-week period in patients with a confirmed diagnosis of RHT. The present analyses aimed to evaluate the BP-lowering effect of aprocitentan in the Black population enrolled in the PRECISION study.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

The PRECISION study was a blinded, randomized, parallel-group, phase 3 study (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03541174) conducted at hospitals or research centers in Europe, North America, Asia, and Australia (Figure S1). The objective was to assess the efficacy of aprocitentan 12.5 and 25 mg for decreasing BP in patients who remained hypertensive despite a standardized background antihypertensive therapy consisting of a single-pill combination of 3 antihypertensives from different classes (amlodipine 5 or 10 mg, valsartan 160 mg, and hydrochlorothiazide 25 mg).

Study Population

The patients included in the present analyses were those participating in the PRECISION study and self-reporting as Black individual. Participants were required to have a history of uncontrolled office BP despite treatment with at least 3 antihypertensive medications within 1 year before screening,[21] and a sitting systolic BP (SBP) ≥140 mm Hg as assessed by unattended automated office BP measurement at trough at all prerandomization visits.

Study Procedures and Treatments

During the screening period (4–12 weeks), the patients were switched from their individual antihypertensive treatments (except β-blockers) to standardized background

antihypertensive therapy. During the subsequent single-blind run-in period (4 weeks), placebo was added. Patients who remained hypertensive were then randomized to aprocitentan 12.5 mg, aprocitentan 25 mg, or placebo once daily in the 4-week part 1. During the 32-week part 2, all patients received aprocitentan 25 mg. In the 12-week part 3, patients were re-randomized to aprocitentan 25 mg or placebo.[21] Adherence to individual antihypertensive treatment was one of the eligibility criteria. Compliance with standardized background antihypertensive therapy was monitored during the entire duration of the study by measurement of valsartan urinary concentrations, and was around 98% during the entire study.

Study Assessments

Unattended office SBP and diastolic BP were assessed at trough at each visit, by averaging 5 sitting BP readings, with the patient resting alone in a quiet place for 5 minutes. Ambulatory BP monitoring (ABPM) over 24 hours was initiated in the morning, at baseline and at weeks 4, 36, and 40. ABPM intervals were selected as daytime (9:00–21:00) and nighttime (1:00–6:00) to avoid transition periods between wake and sleep.[22]

The urine albumin-to-creatinine ratio (UACR) was evaluated at prespecified time points.[21]

Adverse events were recorded throughout the study.

Statistical Analyses

Statistical analyses of the PRECISION study have been described previously.[21] Subgroup analyses for Black individuals were prespecified for primary and key secondary end points using the same mixed model as the main analysis for each subgroup level.

Post hoc analyses were performed to provide additional descriptive summaries for changes in office BP from baseline and for 24-hour, daytime, and nighttime ABPM.

M.S.S. had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

RESULTS

Among the 730 patients enrolled in the PRECISION study, 82 (11%) were Black individual, including 78 patients recruited from the United States, representing 37% of the US participants.[20] Baseline characteristics of these 82 patients were representative of the PRECISION population with RHT, showing a high occurrence of obesity (80% of patients with body mass index ≥30 kg/m^2), CKD defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2 (23%), type 2 diabetes (68%), sleep apnea (28%), and a mean age of 61.3 years (Table 1). At screening, all 82 patients were on at least 3 drug classes (Table S1), and 54% of them were on ≥4 antihypertensive drugs. Among the 57% of patients taking a β-blocker at screening, 89% continued their treatment at randomization. Owing to the small sample size, some imbalance was observed between treatment groups: patients on placebo tended to be older and have a lower estimated glomerular filtration rate than patients on active treatment, while patients on aprocitentan were more likely to be severely obese (Table 1). The baseline characteristics of the patients at re-randomization are provided in Table S2.

In study part 1, after 4 weeks of double-blind treatment, aprocitentan and placebo produced similar reductions in office SBP at trough (least square mean change from baseline: −11.3 mm Hg for the 12.5 mg dose, −11.9 mm Hg for the 25 mg dose, and −12.0 mm Hg for placebo; Figure 1). However, aprocitentan dose-dependently decreased mean 24-hour ambulatory SBP at week 4 (least square mean change from baseline: −4.0 mm Hg at 12.5 mg, −8.6 mm Hg at 25 mg, and −0.7 mm Hg for placebo), with a BP-lowering effect evident during both daytime and nighttime (Figure 2).

During the 32-week part 2, office trough SBP further decreased, reaching a mean reduction of 16.4 mm Hg at week 36 from baseline (Table S3).

In study part 3, office SBP increased with placebo compared with aprocitentan by 9.9 mm Hg (Figure 1). Mean 24-hour, daytime, and nighttime ambulatory SBP increased on placebo by 8.1 mm Hg, 3.4 mm Hg, and 9.7 mm Hg, respectively, compared with aprocitentan (Figure 2). Consistent results were observed for diastolic BP (Figure 1; Table S3 and Figure S2).

Micro- or macroalbuminuria was present at baseline in 43 patients. In patients with albuminuria >30 mg/g, aprocitentan markedly reduced UACR at week 4 by 38% and 65% at 12.5 and 25 mg, respectively, versus 13% for placebo (Table S4). The antiproteinuric effect was sustained during part 2 (−50% at week 36). After 4 weeks of randomized withdrawal, UACR increased by 73% with placebo versus 14% on aprocitentan.

Aprocitentan was well-tolerated in Black patients, with no unexpected safety signals (Table S5).[20] Six adverse events (including 1 fatal event due to COVID-19) led to treatment discontinuation, all during the 32-week part 2, but none for edema/fluid retention during the entire study. Early-occurring edema/fluid retention was the most frequently reported adverse event. During part 1, mild to moderate peripheral edema was reported in 3 patients (10%) receiving aprocitentan 25 mg, but none in the aprocitentan 12.5 mg or placebo groups (Table 2). Over the entire 32-week part 2, 16 patients (20%) had edema/fluid retention (mostly mild to moderate and peripheral). All but 1 had a medical history of cardiometabolic diseases such as peripheral artery disease and diabetes, and most (13/16) were on the higher dose of amlodipine (10 mg daily). One event was associated with a hypertensive episode and was assessed as severe in a patient with a history of preexisting edema, diabetes, and CKD stage 3b. No cases of hyperkalemia related to study treatment were reported. No orthostatic hypotension and no drug-induced hepatotoxicity were observed. Two patients with a medical history of diabetes, CKD or heart failure were hospitalized for heart failure during part 2. One patient (1.3%) with a severe cardiovascular medical history experienced a myocardial infarction.

Table 1. Characteristics of the Randomized Black Patients

Characteristic	Placebo (n=26)	Aprocitentan 12.5 mg (n=28)	Aprocitentan 25 mg (n=28)	All patients (n=82)
Mean age at screening, y	63.3 (10.7)	60.8 (9.2)	59.9 (9.4)	61.3 (9.8)
18–<65	12 (46)	17 (61)	18 (64)	47 (57)
65–<75	9 (35)	9 (32)	8 (29)	26 (32)
≥75	5 (19)	2 (7)	2 (7)	9 (11)
Sex				
Men	14 (54)	16 (57)	12 (43)	42 (51)
Women	12 (46)	12 (43)	16 (57)	40 (49)
Ethnicity				
Hispanic or Latino	1 (4)	4 (14)	0	5 (6)
Geographic area				
Europe	2 (8)	1 (4)	1 (4)	4 (5)
North America	24 (92)	27 (96)	27 (96)	78 (95)
Body mass index at screening, kg/m^2				
Mean	35.1 (5.6)	35.8 (6.5)	37.9 (8.0)	36.3 (6.8)
Low to overweight (<30)	3 (12)	7 (25)	6 (21)	16 (20)
Obese (30–<40)	19 (73)	15 (54)	12 (43)	46 (56)
Severely obese (≥40)	4 (15)	6 (21)	10 (36)	20 (24)
Estimated glomerular filtration rate at baseline, mL/min per 1.73 m^2				
≥60	17 (65)	21 (75)	25 (89)	63 (77)
15–<60	9 (35)	7 (25)	3 (11)	19 (23)
Urine albumin-creatinine ratio at baseline, mg/g				
<30	11 (42)	18 (64)	10 (36)	39 (48)
30–300	10 (38)	6 (21)	10 (36)	26 (32)
>300	5 (19)	4 (14)	8 (29)	17 (21)
Medical history				
Diabetes	19 (73)	18 (64)	19 (68)	56 (68)
Ischemic heart disease	7 (27)	…	2 (7)	9 (11)
Congestive heart failure	2 (8)	1 (4)	2 (7)	5 (6)
Sleep apnea syndrome	8 (31)	8 (29)	7 (25)	23 (28)
Stroke*	3 (12)	…	2 (7)	5 (6)
≥4 w drugs at screening	15 (58)	14 (50)	15 (54)	31 (54)
β-Blocker	17 (65)	14 (50)	16 (57)	47 (57)
Unattended automated office blood pressure at baseline, mm Hg				
Systolic blood pressure	158.4 (10.1)	152.9 (9.6)	156.4 (10.3)	155.9
Diastolic blood pressure	86.4 (9.0)	89.8 (9.5)	86.6 (9.0)	87.6
Ambulatory blood pressure monitoring at baseline, mm Hg†				
24-hour systolic blood pressure	141.9 (12.3)	138.3 (12.3)	145.1 (14.5)	141.8
24-hour diastolic blood pressure	84.8 (7.6)	84.4 (9.45)	86.5 (7.7)	85.2

Data are mean (SD) or n (%), unless otherwise stated.

*Includes ischemic and hemorrhagic strokes and excludes other central nervous system disorders.

†The number of patients with assessed ambulatory blood pressure monitoring at baseline was: 22 (79%) patients for aprocitentan 12.5 and 25 mg; and 23 (88%) patients for placebo.

Aprocitentan 12.5 and 25 mg decreased hemoglobin, which slightly increased on placebo (−6.6 g/L, −8.5 g/L, and +2.2 g/L, respectively). Estimated plasma volume moderately increased with aprocitentan and decreased with placebo (+9.8%, +10.6%, and −2.0%, respectively). Both parameters stabilized during part 2 and reversed on placebo in part 3 (Table S6). Only minimal increases in N-terminal pro-brain natriuretic peptide were observed in part 1 with aprocitentan (+11% at 12.5 and +5% at 25 mg, −2% with placebo) and remained in the same range (+8%) during part 2 (Table S6). Estimated glomerular filtration rate decreased slightly in all 3 groups

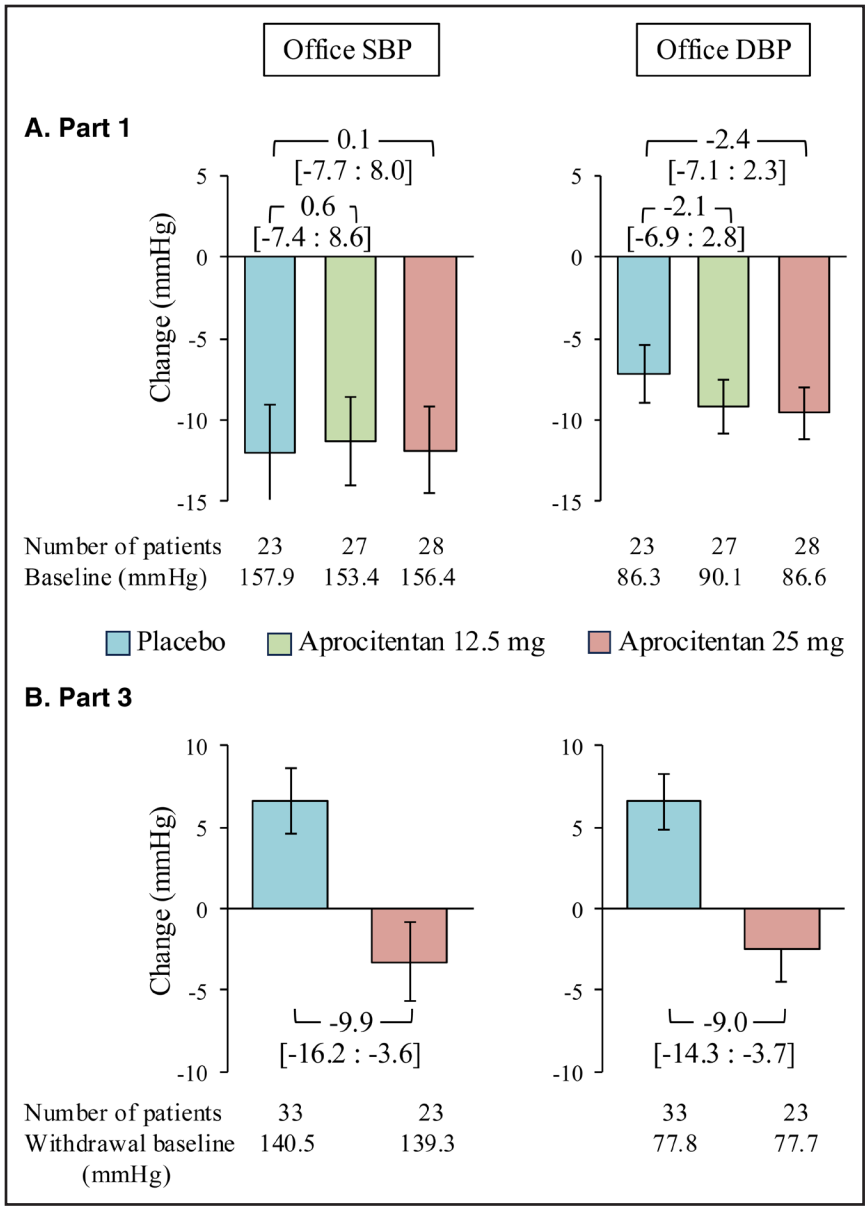

Figure 1. Least square mean changes in systolic blood pressure (SBP) and diastolic BP (DBP).
SBP and DBP were measured as sitting unattended automated office blood pressure from baseline to week 4 in double-blind part 1 (**A**) and from withdrawal baseline (week 36) to week 40 in double-blind withdrawal part 3 (**B**). Least square mean differences from placebo are reported with 95% CIs. Bars represent SEM.

in part 1 and stabilized in parts 2 and 3 (Table S6). No relevant changes in sodium levels were observed during the study (Table S6). Small increases in body weight were observed with aprocitentan (0.03 kg at 12.5 mg, 0.6 kg at 25 mg) during part 1, which reversed during parts 2 and 3 (Table S7). There was a small decrease in heart rate (Table S7).

DISCUSSION

Hypertension in Black individuals can be difficult to control.[23] In the PRECISION study, Black patients with persisting high BP despite treatment with 3 antihypertensive drugs from different classes and a β-blocker in 57% of them, addition of the dual endothelin receptor antagonist aprocitentan showed clinically relevant and durable BP reduction.

The PRECISION study followed rigorous steps to confirm the diagnosis of RHT before randomization. To eliminate pseudo-RHT, the selection of patients included repeated unattended office BP measurements, optimized and standardized antihypertensive background therapy administered as a single-pill triple combination, and control of adherence to treatment by measurement of valsartan concentrations. As a result, >44% of all screened patients with an initial diagnosis of RHT were found to have pseudo- and not confirmed RHT and were not randomized.[21] The design of the study included a placebo-controlled part with 2 doses of aprocitentan to measure its short-term BP-lowering potential on top of background therapy and a double-blind randomized withdrawal part after a long single-blind administration of aprocitentan to demonstrate the durability of the BP-lowering up to 48 weeks. Two methods were chosen to

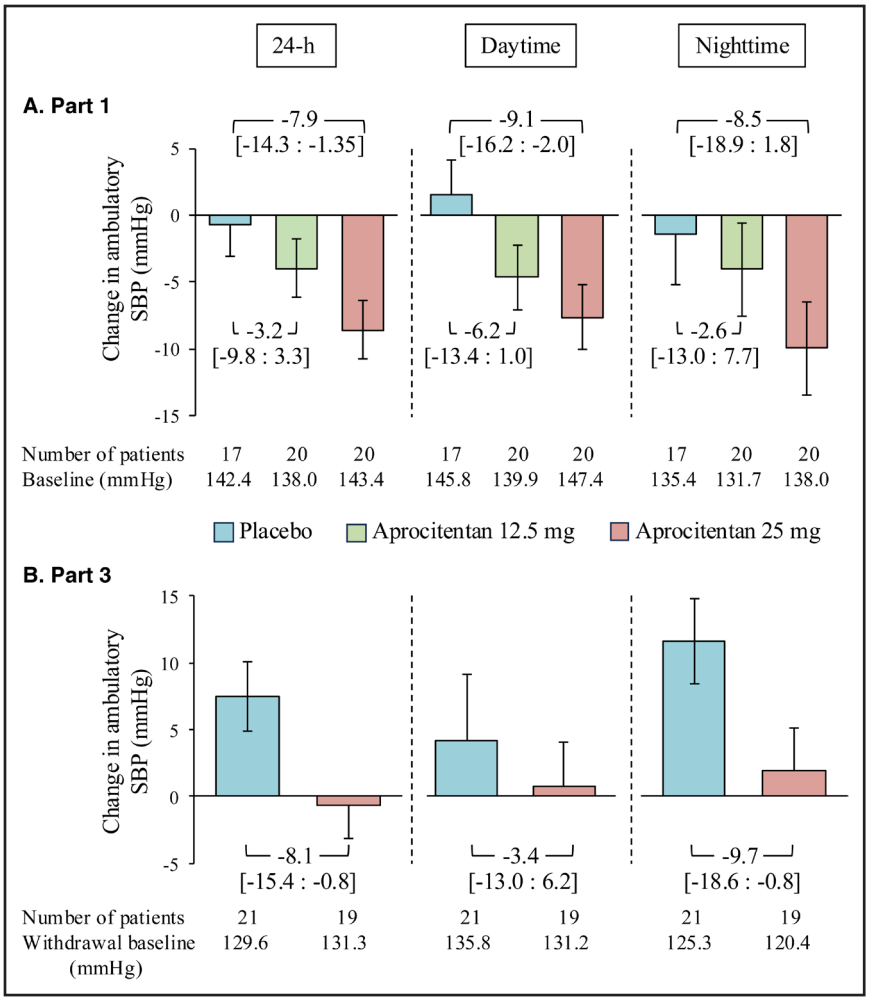

Figure 2. Least square mean changes in 24-hour, daytime, and nighttime ambulatory systolic blood pressure (SBP).
Changes from baseline to week 4 in double-blind part 1 (**A**) and from withdrawal baseline (week 36) to week 40 in double-blind withdrawal part 3 (**B**). Least square mean differences from placebo are reported with 95% CIs. Bars represent SEM. The ANCOVA included a factor for treatment group and a covariate for baseline (or withdrawal baseline).

measure BP, unattended office BP measurements performed in the morning at trough and ABPM.

All patients enrolled in the PRECISION study[20] were high cardiovascular risk patients, a profile consistent with the risk factors for resistance to treatment in hypertension, including high body mass index, older age, type 2 diabetes, CKD, heart failure, and sleep apnea.[4]

The role of an overstimulation of the endothelin system in causing hypertension in people with these multiple risk factors for resistance is supported by: (1) the fact that the endothelin system is upregulated in the presence of each 1 of those risk factors;[11] (2) the characteristics of RHT, supporting a role for endothelin, such as the frequent association with salt sensitivity[4,11] and the resistance to classic drugs that do not target the endothelin system; and (3) the efficacy of aprocitentan in the PRECISION study.[20]

The endothelin system, including plasma endothelin-1, vascular wall endothelin-1, endothelin converting enzyme and ET_B receptors, is indeed upregulated in Black patients with hypertension, when compared with normotensive Black individuals or White patients with hypertension.[12,13] Salt sensitivity in RHT also suggests a role for the endothelin system: endothelin-3 via activation of ET_B receptors on the subfornical organ, increases the sensitivity of the sodium sensor Na_x, central to the regulation of salt intake.[24] Endothelin also inhibits the skin storage of salt[25] and salt increases endothelin production.[25] Endothelin mediates the increase in BP and cardiac hypertrophy induced by salt[26] and is responsible for the increased sensitivity of the basilar artery to calcium in stroke-prone hypertensive rats.[27] Endothelin may actually be a new player to explain increased tubular salt and water reabsorption in Black patients.[14,28] Endothelin increases aldosterone and vasopressin production and dual endothelin receptor blockade suppresses the secretagogue effect of endothelin-1 in human adrenocortical cells.[29–31] Endothelin might also be a key participant in primary hyperaldosteronism,[32] frequent in Black individuals,[33] and associated with high endothelin-1 plasma concentrations.[34]

About one-fourth of the Black patients in the PRECISION study were severely obese with a body mass index ≥40 kg/m^2. Hypertension in obese patients is also associated with endothelin, and a genetic polymorphism in the prepro-endothelin-1 gene, described as a G-to-T transversion and a lysine/asparagine change in the protein, is strongly associated with high body mass index in the determination of BP levels.[35]

Table 2. Treatment-Emergent Adverse Events of Special Interest

Prespecified MedDRA query name	Placebo	Aprocitentan, 12.5 mg	Aprocitentan, 25 mg
Part 1: double-blind	(n=25)	(n=28)	(n=29)
Edema/fluid retention	0	0	3 (10.3)
Need for diuretics	0	0	2 (6.9)
Decompensation/aggravation of heart failure	0	0	0
Anemia	0	1 (3.6)	1 (3.4)
Hepatic disorder	0	-	-
Part 2: single-blind			(n=80)
Edema/fluid retention			16 (20.0)
Need for diuretics			5 (6.3)
Decompensation/aggravation of heart failure			3 (3.8)*
Anemia			7 (8.8)
Hepatic disorder			1 (1.3)†
Part 3: double-blind withdrawal	(n=35)		(n=30)
Edema/fluid retention	0		0
Need for diuretics	0		0
Decompensation/aggravation of heart failure	0		0
Anemia	0		0
Hepatic disorder	1 (2.9)		0

Data are n or n (%). Events are defined using MedDRA, version 24·1. Safety analyses were performed by received treatment groups.

*Two hospitalizations for heart failure and 1 for myocardial infarction.

†Isolated increase in alkaline phosphatase in the context of worsening of kidney function of mild intensity.

When BP was measured using ABPM, the placebo-corrected effect of aprocitentan at week 4 was marked in the Black patients, and it was strong at every time point of the 24-hour recording. In the randomized double-blind withdrawal part, both BP measuring methodologies equally confirmed the sustained BP-lowering effect of aprocitentan. The efficacy of aprocitentan in the Black population is supported by the totality of these data. The neutral effect of aprocitentan on trough office BP versus placebo at 4 weeks was likely due to the large placebo effect (−12.0 mm Hg), which may have blunted, together with intraperson BP variability, the differences in office SBP between the aprocitentan and placebo groups in the Black subgroup. A similar placebo effect (−11.5 mm Hg) was observed for the general population enrolled in the PRECISION study.[20] In that study, it did not prevent demonstrating a statistically significant effect due to the large sample size (n=730), but this was not the case in the present analysis with a smaller subgroup (n=82). The placebo effect with ABPM was much smaller than with office measurement, as seen in the PRECISION study and in line with the literature.[36] This could be because ABPM results from repeated day and night BP measurements over 24 hours in the patient's familiar surroundings, whereas trough office BP is measured only 5× in a short period in an unfamiliar environment. Therefore, ABPM may be more reliable for assessing the effect of a drug, particularly when a small sample size is considered. ABPM, however, was not chosen as the primary end point to minimize the risk of missing data.

The strong nighttime BP effect of aprocitentan is helped by its long half-life,[16] but more importantly may be due to a sympatholytic effect of aprocitentan. Because endothelin, via ET_A and ET_B receptors, causes catecholamine release and increases baroreceptor function,[37] sympatholytic and baroreceptor-buffering actions of aprocitentan likely played a role in its impressive efficacy on nighttime BP. These results might have favorable prognostic implications given the high prevalence of nocturnal hypertension in Black individuals[38] and the strong association between nighttime BP and cardiovascular risk.[39]

Finally, aprocitentan notably decreased UACR. Dual ET_A/ET_B receptor antagonists markedly reduced proteinuria in animal models at doses reducing BP, decreasing intraglomerular pressure by preferential postglomerular vasodilation, protecting the glomeruli, and also decreasing renal vascular hypertrophy, fibrosis, and inflammation in the kidney.[40–44] A potential renal protective effect of aprocitentan in the Black population, as in the overall population, should be investigated in a dedicated study in patients with CKD.

Aprocitentan was safe and well-tolerated over the 48 weeks of the study, even in the 23% of patients with CKD, with no or low reports of headaches and orthostatic hypotension, no heart rate increases despite the BP lowering, no treatment-related hyperkalemia, and only 1 severe case of edema in the context of a hypertensive episode in a patient with high cardiovascular risk factors. There were cases of peripheral edema, which had not been seen with monotherapy in phase 2,[19] and may have been increased in number by the high cardiovascular morbidities reported for the recruited patients, the high dose of amlodipine used in most of these patients, and some aspects of the protocol, such as switch from loop diuretics to hydrochlorothiazide. Fluid retention, and not only peripheral edema, has been a concern with ET_A selective receptor antagonists,[45] and the development of many ET_A selective antagonists has been stopped[46,47] or their dose for clinical use has been dramatically reduced.[48,49] Dual blockade of both ET_A and ET_B receptors, as achieved with aprocitentan may have a potential for less severe fluid retention, by preventing endothelin-1 from activating ET_B receptors,[50] avoiding vascular permeability increase[50] and, in humans, causing no sodium retention.[51] This may be particularly relevant in pathological conditions such as hypertension, where the expression of ET_B receptors is shifted from endothelial toward vascular smooth muscle cells.[52,53] This may explain the benign character of the reported edema events and the absence of significant increases in N-terminal pro-brain natriuretic peptide with aprocitentan.

The main limitation of this article is the low sample size for this preplanned subgroup analysis. This probably

led to the observed imbalance in baseline characteristics (notably for UACR) of the 3 treatment groups. As a probable consequence, the treatment effect did not consistently reach the treatment effect observed in the PRECISION study. The small sample size also reduced the precision of observed treatment effects, resulting in wide 95% CIs. Nevertheless, the totality of results from this preplanned investigation was in line with results observed in the overall PRECISION population.

In conclusion, this investigation focusing on the Black patients enrolled in the PRECISION study showed that aprocitentan lowered BP in this population with RHT despite treatment with at least 3 antihypertensive drugs, including a diuretic. Aprocitentan rapidly decreased BP and had a sustained effect until the end of the study. Aprocitentan also lowered albuminuria in patients already treated with an angiotensin blocker. Aprocitentan may represent a new therapeutic approach with an additional mechanism of action particularly fitting the pathophysiology of hypertension in Black adults with uncontrolled drug-treated hypertension.

PERSPECTIVES

Aprocitentan was approved for the treatment of RHT by the European Medicines Agency in March 2024 and by the UK Medicines and Healthcare Regulatory Agency in January 2025. Aprocitentan was approved by the Food and Drug Administration in March 2024. The European Medicines Agency and the UK Medicines approved the 12.5 and 25 mg doses for the treatment of RHT, and the Food and Drug Administration approved the 12.5 mg dose for the treatment of hypertension in combination with other antihypertensive drugs when BP is not adequately controlled. Aprocitentan works by antagonizing the actions of endothelin. Endothelin and its receptors are present in the heart, kidney, and vessels, and when upregulated in pathology, they cause vasoconstriction, inflammation, and remodeling.

Hypertension in Black patients is particularly difficult to control. This may be because their hypertension is related to the upregulation of the endothelin system, which to date had not been addressed by any existing antihypertensive drugs.

The preplanned analyses of the phase 3 PRECISION study in the group of Black patients with confirmed RHT suggest that treatment with aprocitentan produces clinically meaningful and sustained BP reductions and a decrease in proteinuria in this population.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S7
Figures S1 and S2

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