Clinical Trial

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Randomized Dose-Response Study of the New Dual Endothelin Receptor Antagonist Aprocitentan in Hypertension

Pierre Verweij, Parisa Danaietash, Bruno Flamion, Joël Ménard, Marc Bellet

Abstract—This study examined the dose-response characteristics of aprocitentan, a dual endothelin A/endothelin B receptor antagonist, in patients with essential hypertension. In a randomized, double-blind, parallel study design, eligible patients with a sitting diastolic blood pressure (BP) of 90–109 mm Hg received aprocitentan 5, 10, 25, or 50 mg, placebo, or lisinopril 20 mg as a positive control once daily for 8 weeks. Multiple automated office BP readings were obtained with patients resting unattended (unattended automated office BP) at baseline, weeks 2, 4, and 8. Ambulatory BP was monitored for 24 hours at baseline and week 8. After a single-blind placebo run-in period, 490 eligible patients were randomized to the double-blind phase, with 409 patients completing 8 weeks of therapy per protocol. Aprocitentan 10, 25, and 50 mg decreased sitting systolic/diastolic unattended automated office BP from baseline to week 8 (placebo-corrected decreases: 7.05/4.93, 9.90/6.99, and 7.58/4.95 mm Hg, respectively, $P \leq 0.014$ versus placebo), compared with an unattended automated office BP reduction of 4.84/3.81 mm Hg with lisinopril 20 mg. For patients with valid ambulatory BP, aprocitentan 10, 25, and 50 mg significantly decreased placebo-corrected 24-hour BP by 3.99/4.04, 4.83/5.89, and 3.67/4.45 mm Hg, respectively. Incidence of adverse events was similar in the aprocitentan groups (22.0%–40.2%) and the placebo group (36.6%). Aprocitentan produced dose-dependent decreases in hemoglobin, hematocrit, albumin, and uric acid, an increase in estimated plasma volume, but no change in weight versus placebo. These findings support further investigation of aprocitentan at doses of 10 to 25 mg in hypertension.

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Key Words: aprocitentan ■ blood pressure ■ endothelin ■ essential hypertension

Many hypertensive adults still fail to achieve their recommended blood pressure (BP) targets despite steady improvement in hypertension awareness, treatment, and control rates over the last 30 years.[1] Therefore, novel antihypertensive drugs, especially those that can be combined with existing therapies, can be highly valuable.[2]

ET (endothelin)-1 is a potent vasoconstrictor peptide, a causative agent in endothelial dysfunction, a growth factor, and a stimulant of aldosterone synthesis and catecholamine release.[3,4] Blockade of its receptors has demonstrated efficacy in numerous models of hypertension, especially in low-renin/salt-sensitive conditions.[5,6] Orally administered ET receptor antagonists (ERAs) have been investigated in hypertension. While bosentan efficiently decreased BP in patients with hypertension,[7] its hepatotoxic effects have impeded further development in this indication. Initially promising results with darusentan in patients with resistant hypertension[8] have not been confirmed.[9] Furthermore, ERAs have been associated with fluid retention in patients with renal and heart failure.[10,11]

Aprocitentan is a potent, orally active, dual endothelin A/endothelin B (ETA/ETB) receptor antagonist with an ETA/ETB inhibitory potency ratio of 1:16.[6,12] Based on this, aprocitentan is positioned very close to the International Union of Basic and Clinical Pharmacology (IUPHAR)-reference dual ERA bosentan.[13] Aprocitentan has a long half-life (44 hours) in humans.[12] Unlike bosentan, but like macitentan,[14] aprocitentan does not interfere with bile salt homeostasis and does not cause hepatotoxicity. Based on studies in rodents, dual blockade of ETA/ETB receptors appears to have a lower risk of fluid retention and vascular leakage than ETA-selective blockade, which, by overstimulation of ETB receptors, results in nonselective vasodilation and vasopressin release.[15] Furthermore, in animal models of hypertension, combining aprocitentan with renin-angiotensin-aldosterone system inhibitors or calcium channel blockers has additive or synergistic

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effects on BP, suggesting that aprocitentan could be combined with other antihypertensives.[6]

The present study examined the dose-response relationship of aprocitentan monotherapy in patients with essential hypertension. A unique feature of this dose-finding study was the use of unattended automated office BP (uAOBP) measurement.

Methods

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

Study Design

This was a randomized, double-blind, multicenter, placebo, and active comparator-controlled trial designed to evaluate the efficacy and safety of once-daily aprocitentan 5, 10, 25, and 50 mg in patients with grade 1 to 2 essential hypertension. Lisinopril 20 mg once daily served as a positive control.[16]

After initial screening, patients entered a 4- to 6-week single-blind, placebo run-in period to eliminate the effects of any previous antihypertensive therapy. Eligible patients were then randomly assigned to placebo, aprocitentan, or lisinopril treatment groups. After 8 weeks of double-blind treatment, all patients entered a 2-week single-blind, placebo withdrawal period. Randomization was implemented by Interactive Response Technology and performed using a central randomization list, unstratified and with a block size of 6, generated and kept by a group external to the study sponsor.

Patients

Patients were recruited from 99 sites in Canada, Israel, and the United States between December 2015 and December 2016. Before enrollment, all patients signed consent forms approved by regional institutional review boards. The protocol conformed to the Declaration of Helsinki.

Patients 18 to 75 years of age with a diagnosis of hypertension underwent randomization if their mean sitting diastolic BP (SiDBP) was ≥90 to <110 mm Hg as recorded by uAOBP and if compliance was ≥80% during the placebo run-in period.

Exclusion criteria included secondary hypertension, cardiovascular diseases, diabetes mellitus, renal impairment (estimated glomerular filtration rate <30 mL/(min·1.73 m^2), elevated aminotransferases, hemoglobin <10 g/dL, and psychiatric disorders. Antihypertensive drugs or concomitant medications known to affect BP were not permitted during the study.

Medication Dosing

Patients in the aprocitentan 5, 25, and 50 mg groups received one aprocitentan capsule and one placebo capsule matching lisinopril, whereas patients in the aprocitentan 10 mg group received two 5 mg capsules. Patients allocated to lisinopril received one lisinopril capsule (20 mg) and one placebo capsule matching aprocitentan. The aprocitentan and lisinopril capsules were similar in appearance. Patients were instructed to take 2 capsules in the morning, except on the days of study visits when the medication was to be taken after clinical assessments were conducted.

Study Assessments

Unattended AOBP measurements were performed at all visits using an automatic, oscillometric sphygmomanometer (BpTRU; VSM MedTech, Canada).

BP readings were performed 6× at 1-minute intervals in the same arm after the patient was seated alone for 5 minutes. The mean of the last 5 uAOBP readings was used in the analyses. Every effort was made to ensure that the BP readings were taken 24 hours after the previous dose of study medication (ie, at trough) and before performing any procedures.

Ambulatory BP monitoring (ABPM) was performed for 24 hours at baseline and at week 8 with a Mobil-o-Graph (IEM GmbH, Germany) recorder. Systolic BP (SBP) and diastolic BP (DBP) were measured every 20 minutes from 06:00 to 23:00 and every 30 minutes from 23:00 to 06:00. Monitoring was initiated between 06:00 and 11:00.

Adverse events (AEs) and serious AEs were recorded throughout the study. Clinical laboratory data and vital signs were measured at all study visits.

Statistical Analyses

The primary end point was the change in mean trough SiDBP measured by uAOBP from baseline (ie, at randomization) to week 8. The main analysis was performed using the per-protocol set, which included all randomized patients without protocol deviations interfering with the primary end point (Table S1 in the online-only Data Supplement). A supportive analysis was performed in all randomized patients (using last observation carried forward to impute missing week 8 values, if applicable).

Multiple Comparison Procedure (MCP)–Modeling[17,18] was used to model the dose-response relationship for the primary end point. This approach has been applied in various clinical settings, including hypertension,[19] and has been recognized as an efficient statistical methodology for dose-finding studies by regulatory agencies.[20,21]

In the MCP-Modeling approach, the presence of a dose-response signal is initially tested using a set of prespecified dose-response models (the MCP step at a 1-sided significance level of 0.025, adjusted for multiplicity). Then the dose-response curves are estimated (the Modeling step).

Six possible models were prespecified: linear, linear in log dose, Emax, sigmoidal Emax, logistic, and quadratic. These models assume a monotone dose-response relationship, except for the quadratic model observed previously in hypertension.[19] Model fit was assessed based on Akaike Information Criterion. The analysis was performed using the R-package DoseFinding.[22]

The analysis was also performed for the secondary end point, change from baseline to week 8 in mean trough sitting SBP (SiSBP).

Additionally, an ANCOVA was performed for the changes from baseline to week 8 in SiDBP and SiSBP, each with a factor for treatment group and a covariate for baseline value. The Dunnett test was used to adjust for multiple comparisons.

The ABPM analyses were based on a subset of patients with a valid ABPM at baseline and week 8 (≥14 readings during the day [9:00–21:00] and ≥7 during the night [01:00–06:00]). Definitions of day and night were based on criteria proposed by the European Society of Hypertension.[23]

All ABPM readings recorded during the 24-hour monitoring period were averaged per patient (24-hour mean) using the trapezoidal rule to account for unequal time intervals between measurements. Mean daytime and nighttime ABPM values were calculated similarly. The resulting data were analyzed using the ANCOVA described above, but without correction for multiplicity.

Changes from baseline to week 8 in hemoglobin were modeled in the same way as the changes from baseline in mean trough SiDBP and SiSBP. Changes from baseline in hematocrit, albumin, and estimated plasma volume (PV, based on changes in hemoglobin and hematocrit[24]) were evaluated descriptively.

Assuming a maximum difference versus placebo of 5 mm Hg and an SD of 9 mm Hg for the change from baseline in SiDBP, we calculated that 70 patients per group would provide 90% power to detect a dose-response with MCP-Modeling in the per-protocol set (420 patients). Accounting for 20% exclusion from the per-protocol set, 540 patients were to be randomized. Following a prespecified blinded sample size reestimation (based on an overall SD=8.8 mm Hg observed in the first 119 patients), the size of the per-protocol set was reduced to 66 patients per group. Also accounting for less exclusion from the per-protocol set (17%), the sample size was reduced to 480 patients.

Results

Patients

Of 1659 initially screened patients, 996 were enrolled in the placebo-run-in period, and 490 were randomized (Figure 1).

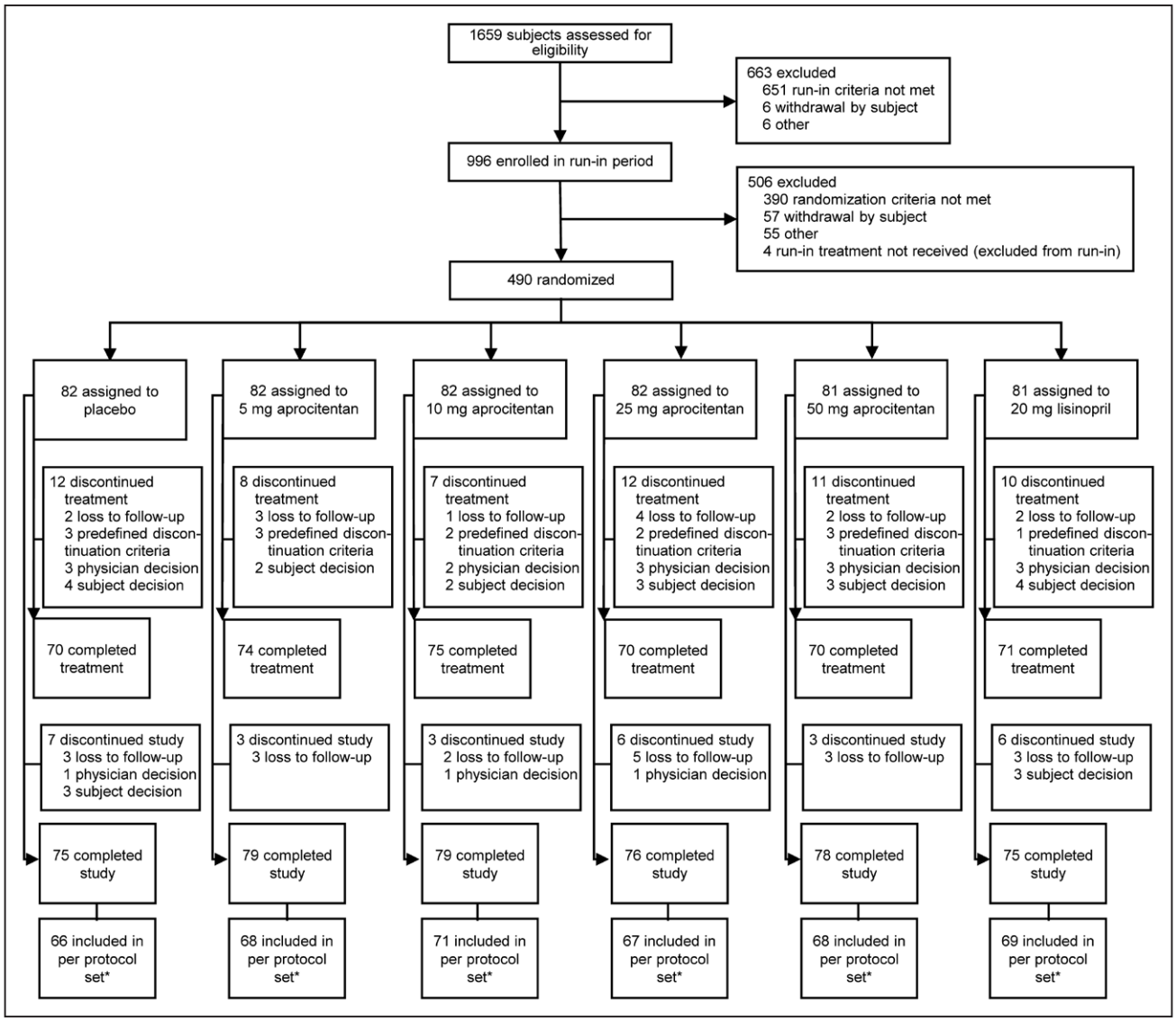

Figure 1. Disposition of patients during the trial. *For protocol deviations see online-only Data Supplement.

The most common reason for exclusion before randomization was failure to meet the SiDBP inclusion criterion. A total of 430 patients completed the 8-week treatment period. Patients were discontinued due to development of grade 3 hypertension defined as SiSBP≥180 or SiDBP≥110 mm Hg (2.4%–3.7% in the aprocitentan groups, 3.7% for placebo, 1.2% for lisinopril), AEs (0%–2.4% aprocitentan, 3.7% placebo, 1.2% lisinopril), or lost to follow-up (1.2%–4.9% aprocitentan, 2.4% placebo, 2.5% lisinopril).

Demographic and baseline characteristics were similar across the 6 treatment groups (Table 1 for the all randomized set, Table S2 for the per-protocol set). The randomized study population was predominantly male (61%), and the mean age was 55 years. The median duration of essential hypertension was 6.8 years. The mean uAOBP at baseline (SiSBP/SiDBP) was 149.8/97.8 mm Hg, and the mean baseline 24-hour BP was 141.6/91.1 mm Hg. Kidney function was normal at baseline (Table 1, Table S2).

uAOBP Measurement

The uAOBP analyses were based on the per-protocol set (n=409). A clinically relevant decrease in trough BP occurred within 2 weeks in the aprocitentan 10, 25, and 50 mg groups and was maintained up to week 8 (Figure 2A and 2B, Table 2). BP returned to placebo levels during the withdrawal period, suggesting the absence of a rebound effect. Of note, the percentage of patients with a SiDBP below 90 mm Hg at week 8 was 44.1%, 52.1%, 64.2%, and 57.4% for aprocitentan 5, 10, 25, and 50 mg, respectively, versus 33.3% and 55.1% for placebo and lisinopril 20 mg, respectively.

The dose-response relationship for the change in mean trough SiDBP from baseline to week 8 was statistically significant ($P<0.001$ for all 6 prespecified dose-response models). A quadratic model (Figure 3A) fitted the data best (Table S3). According to this model, the maximum effect (versus placebo) is reached at a dose of 31 mg (95% bootstrap confidence

Table 1. Demographic and Other Baseline Characteristics (All Randomized Set, N=490)

Characteristics	Placebo	Aprocitentan				Lisinopril
		5 mg	10 mg	25 mg	50 mg	
	n=82	n=82	n=82	n=82	n=81	n=81
At screening						
Age	53.5 (9.1)	54.1 (8.5)	55.3 (9.8)	55.1 (10.0)	54.2 (9.3)	56.0 (9.0)
<65 y	74 (90.2)	74 (90.2)	64 (78.0)	67 (81.7)	69 (85.2)	68 (84.0)
Sex						
Male	55 (67.1)	48 (58.5)	51 (62.2)	45 (54.9)	53 (65.4)	45 (55.6)
Race						
Black	31 (37.8)	28 (34.1)	26 (31.7)	35 (42.7)	26 (32.1)	32 (39.5)
White	48 (58.5)	54 (65.9)	53 (64.6)	46 (56.1)	55 (67.9)	46 (56.8)
Other	3 (3.7)	0	3 (3.7)	1 (1.2)	0	3 (3.7)
Weight, kg	92.0 (18.9)	88.6 (16.9)	90.1 (18.3)	91.1 (16.9)	87.5 (15.8)	87.0 (17.2)
BMI, kg/m^2	30.6 (5.1)	30.1 (4.6)	30.7 (4.5)	31.0 (4.2)	30.2 (4.6)	30.4 (4.6)
Previous antihypertensive treatment	57 (69.5)	56 (68.3)	45 (54.9)	49 (59.8)	54 (66.7)	56 (69.1)
Country						
Canada	3 (3.7)	1 (1.2)	6 (7.3)	4 (4.9)	2 (2.5)	5 (6.2)
Israel	4 (4.9)	6 (7.3)	2 (2.4)	5 (6.1)	4 (4.9)	5 (6.2)
United States	75 (91.4)	75 (91.5)	77 (90.3)	73 (89.0)	75 (92.6)	71 (87.6)
At baseline (randomization)						
SiSBP/SiDBP, mm Hg	149.0/97.9	148.2/97.4	150.5/97.8	152.0/98.4	149.3/98.4	149.7/96.8
	(13.5/5.6)	(14.6/5.2)	(12.3/4.2)	(13.6/5.0)	(13.1/5.2)	(13.7/4.6)
Hemoglobin, g/dL	14.3 (1.2)	14.1 (1.5)	14.2 (1.5)	14.2 (1.5)	14.2 (1.4)	13.9 (1.4)
Hematocrit, %	44.2 (3.6)	43.1 (4.0)	43.5 (4.3)	43.6 (4.1)	43.5 (3.8)	42.7 (4.3)
Albumin, g/L	44.5 (2.3)	43.9 (2.6)	44.1 (2.5)	43.7 (2.8)	44.2 (2.1)	43.3 (2.5)
Estimated glomerular filtration rate, mL/(min·1.73 m^2)	93.5 (15.4)	92.7 (16.8)	94.7 (18.9)	93.1 (20.8)	94.6 (19.6)	94.7 (19.1)

Values are means (SD) for continuous variables; n (%) for categorical variables. BMI indicates body mass index; and SiSBP/SiDBP, sitting systolic/diastolic blood pressure.

interval: 28–37 mg), and half of this effect is reached at a dose of approximately 10 mg.

These results were confirmed by the analysis of the change from baseline to week 8 in mean trough SiSBP (Figure 3B) and by the analysis performed for all randomized patients (Figure S1).

Overall, BP reductions from baseline were greater in white patients (P=0.0084 and P=0.037, for SiSBP and SiDBP, respectively) but did not reach statistical significance for female versus male patients (P=0.18 and P=0.27, for SiSBP and SiDBP, respectively; Table S4a and S4b). However, treatment by subgroup interactions was not statistically significant.

Ambulatory BP Monitoring

The ABPM analyses were based on a subset of the per-protocol set with a valid ABPM at baseline and at week 8 (n=281). As compared to placebo, aprocitentan doses of 10, 25, and 50 mg lowered mean 24-h SBP/DBP from baseline by 3.99/4.04, 4.83/5.89, and 3.67/4.45 mm Hg, respectively (Table 3). Similar trends were observed for daytime and nighttime mean SBP/DBP (Table S5).

Safety and Tolerability

Aprocitentan was generally well tolerated (Table S6); the incidence of AEs (ranging from 22.0% to 40.2% in the various dose groups) was similar to that reported for placebo (36.6%). Overall, the most common events were hypertension, headache, and nasopharyngitis. None of the 3 serious AEs were considered to be related to treatment. Numerically fewer patients reported AEs leading to discontinuation in the aprocitentan groups (1.2%–3.7%) than in the placebo group (6.1%; P=0.14), with 3.7% in the lisinopril group (P=0.65).

Mild-to-moderate peripheral edema was reported in 4 patients (2 each in the 25 mg and 50 mg groups) and led to permanent discontinuation from treatment in 2 patients (in the 50 mg group). One of these 2 patients had a history of ankle edema. Among the 4 patients with edema, 3 had a weight change of 0.0 to 1.1 kg and hemoglobin reductions of 0.5 to

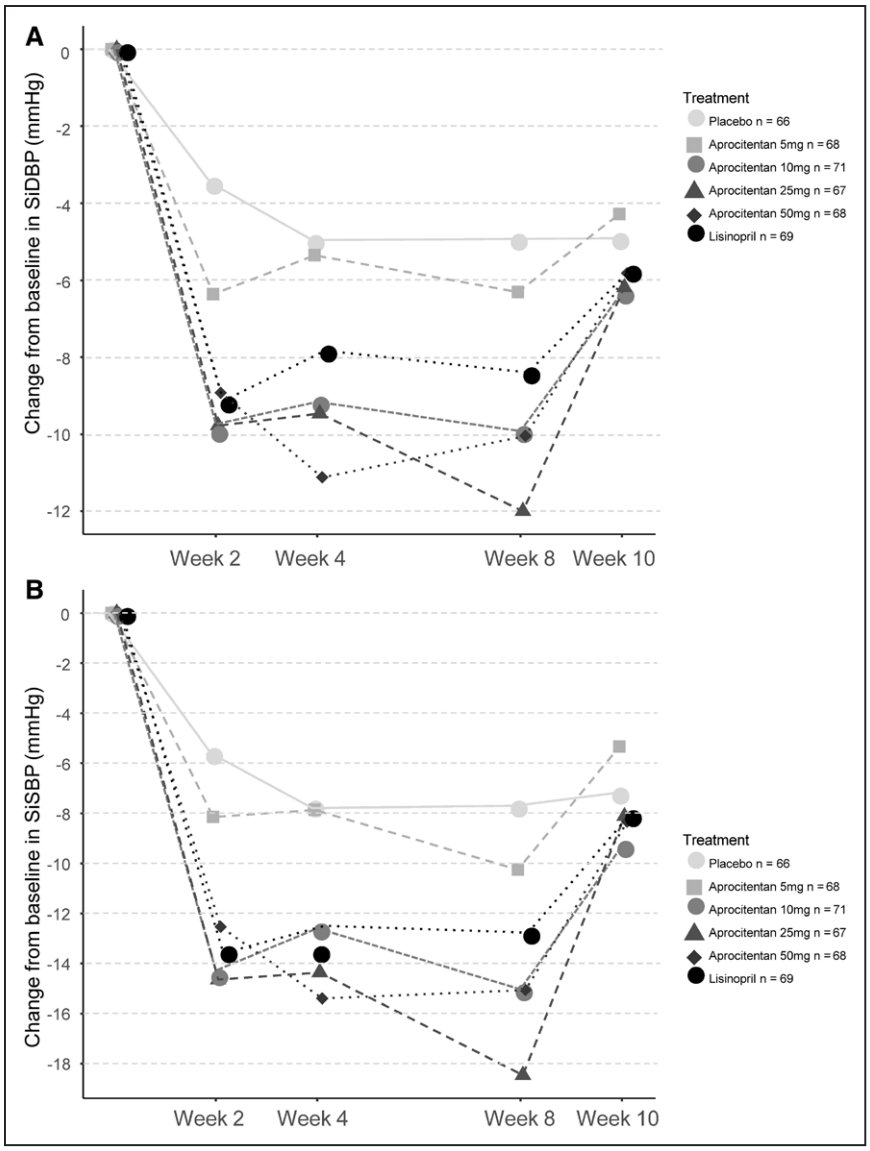

Figure 2. Change in unattended automated office blood pressure. Mean change from baseline in (**A**) sitting diastolic blood pressure (SiDBP) and (**B**) sitting systolic blood pressure (SiSBP) over time (per-protocol set, n=409).

1.4 g/ dL, suggesting minimal fluid retention and hemodilution and possible fluid redistribution. The fourth patient had an initial weight of 123.8 kg, which increased by 3.9 kg during the screening and run-in period. The patient had a further weight increase of 5.5 kg during treatment, accompanied by an increase in hemoglobin of 1 g/dL and thus no sign of hemodilution.

Liver aminotransferases >3× the upper limit of the normal range occurred in 1 patient receiving placebo and 1 patient receiving aprocitentan 5 mg.

Hemoglobin and Estimated PV

All aprocitentan doses lowered hemoglobin, hematocrit, and albumin from baseline to week 8, and there was a dose-dependent increase in estimated PV from baseline (Table S7). However, there was little or no change in body weight (–0.04 to +0.41 kg in aprocitentan groups versus +0.33 and –0.28 kg in the placebo and lisinopril groups, respectively).

The dose-response analysis for hemoglobin differed from the analyses for BP in that a linear in log dose model fitted the data best (Figure 3C); every doubling of the aprocitentan dose resulted in a fixed decrease in hemoglobin of ≈0.125 g/dL.

Of note, serum urate decreased in a dose-dependent manner in the aprocitentan groups (Table S7; $P<0.001$).

Discussion

Principal Findings

This is the first clinical trial conducted with the dual ETA/ETB receptor antagonist aprocitentan in essential hypertension. Two novel aspects of this study were the use of uAOBP in a dose-response hypertension study and the use of MCP-Modeling to model the dose-response relationship. Aprocitentan 10, 25, and 50 mg once daily lowered BP in a clinically relevant, dose-dependent manner as measured by uAOBP and ABPM. In line with previous results from Gomez et al,[16] a reduction in BP was also observed with lisinopril. These findings suggest that the difference in treatment effect between the 25 mg dose of this new ERA compared with an angiotensin-converting enzyme inhibitor at its currently prescribed dose is approximately –5/–3 mm Hg. The absolute BP reductions with aprocitentan are in the ranges previously

Table 2. Change From Baseline to Week 8 in Unattended Automated Office BP (Per-Protocol Set, n=409)

		Aprocitentan				
	Placebo	5 mg	10 mg	25 mg	50 mg	Lisinopril
Unattended Automated Office BP	n=66	n=68	n=71	n=67	n=68	n=69
Sitting systolic BP at trough, mm Hg						
Baseline	149.2	149.4	149.8	151.2	148.6	149.8
	(13.1)	(13.9)	(12.7)	(13.7)	(12.8)	(14.2)
Change from baseline to week 8	–7.7	–10.3	–15.0	–18.5	–15.1	–12.8
	(18.8)	(15.3)	(14.5)	(15.0)	(11.8)	(16.0)
Placebo-corrected	…	–2.45	–7.05	–9.90	–7.58	–4.84
95% CI*	…	–8.44 to 3.54	–12.98 to –1.12	–15.92 to –3.88	–13.58 to –1.59	–10.49 to 0.82
P value*		0.707	0.014	<0.001	0.008	0.093
Sitting diastolic BP at trough, mm Hg						
Baseline	97.5	97.8	97.7	97.8	98.2	96.8
	(5.4)	(5.5)	(4.3)	(4.8)	(5.3)	(4.6)
Change from baseline to week 8	–4.9	–6.3	–9.9	–12.0	–10.0	–8.4
	(11.1)	(8.9)	(8.7)	(8.2)	(7.9)	(9.6)
Placebo-corrected	…	–1.31	–4.93	–6.99	–4.95	–3.81
95% CI*	…	–5.10 to 2.49	–8.68 to –1.17	–10.80 to –3.19	–8.75 to –1.15	–7.26 to –0.37
P value*		0.812	0.005	<0.001	0.006	0.030

Values are means (SD) unless otherwise stated. BP indicates blood pressure.
*Dunnett correction for testing multiple aprocitentan doses vs placebo.

established as a surrogate for reduction in cardiovascular morbidity and mortality in patients with hypertension.[25]

The time course of the reduction in BP with aprocitentan showed that most of the antihypertensive effect was achieved within week 2 and that the prolonged, 24-hour duration of the antihypertensive effect supports a once-daily dosing regimen. In addition, the long half-life of aprocitentan (44 hours[12]) is advantageous as it should maintain a decrease in BP following a missed dose.[26] There were no clinically important differences in the incidence of AEs between the aprocitentan doses and placebo or lisinopril in this 8-week trial.

Primary End point and Analysis

We chose uAOBP measurements for the primary end point as they are less variable than routine office BP measurements due to reduced white-coat effect and provide a better estimate of an individual's BP status than routine office BP measurements.[27,28] Mean systolic uAOBP measurements are comparable to the mean awake ambulatory BP, 7 mm Hg lower than office BP in research studies, and 14 mm Hg lower than readings obtained in routine clinical practice.[29]

The placebo effect of SiDBP measured with uAOBP (–4.9 mm Hg) was smaller than that observed with office BP in similar studies (eg,–8.6 mm Hg in an aliskiren multicenter trial[30]). Nonetheless, the placebo effect was still fairly large, probably because uAOBP was used for inclusion. SiDBP is also likely to decrease in the placebo group because of regression to the mean.[31]

ABPM was used as a secondary end point. One advantage of using ABPM compared with office BP is that the placebo effect is usually smaller.[32] Therefore, ABPM has been suggested as the preferred device for clinical therapeutic trials.[33] In this phase 2 study, exploratory analyses based on ABPM resulted in dose-response curves with a similar shape as for uAOBP. However, uAOBP is less burdensome and can be performed at each visit, thus providing more information for a dose-finding study.

Another novel aspect of this trial was the use of a model-based approach. A quadratic model was most appropriate for the BP data and showed that the maximum effect was reached at a dose of ≈30 mg, and half of the effect at ≈10 mg. We have no explanation for the apparent reduction in efficacy at the 50 mg dose; it may reflect a plateauing of the dose-response between 25 and 50 mg. Although aprocitentan has vasodilator properties, and other vasodilators have been shown to induce counter-regulatory neurohumoral activation at high doses in patients with hypertension,[34] aprocitentan, like other dual ERAs, has not been shown to activate the neurohumoral system.[7]

Safety and Tolerability

The favorable effects of aprocitentan on BP are further supported by the known safety profile of the dual ERA bosentan that is based on its extensive use in pulmonary arterial hypertension.[35] In this population, the most relevant AE associated with this drug class is fluid retention.[11] The present study reported only 4 cases of peripheral edema. Dose-dependent reductions in hemoglobin and hematocrit and an increase in estimated PV were observed with aprocitentan as early as

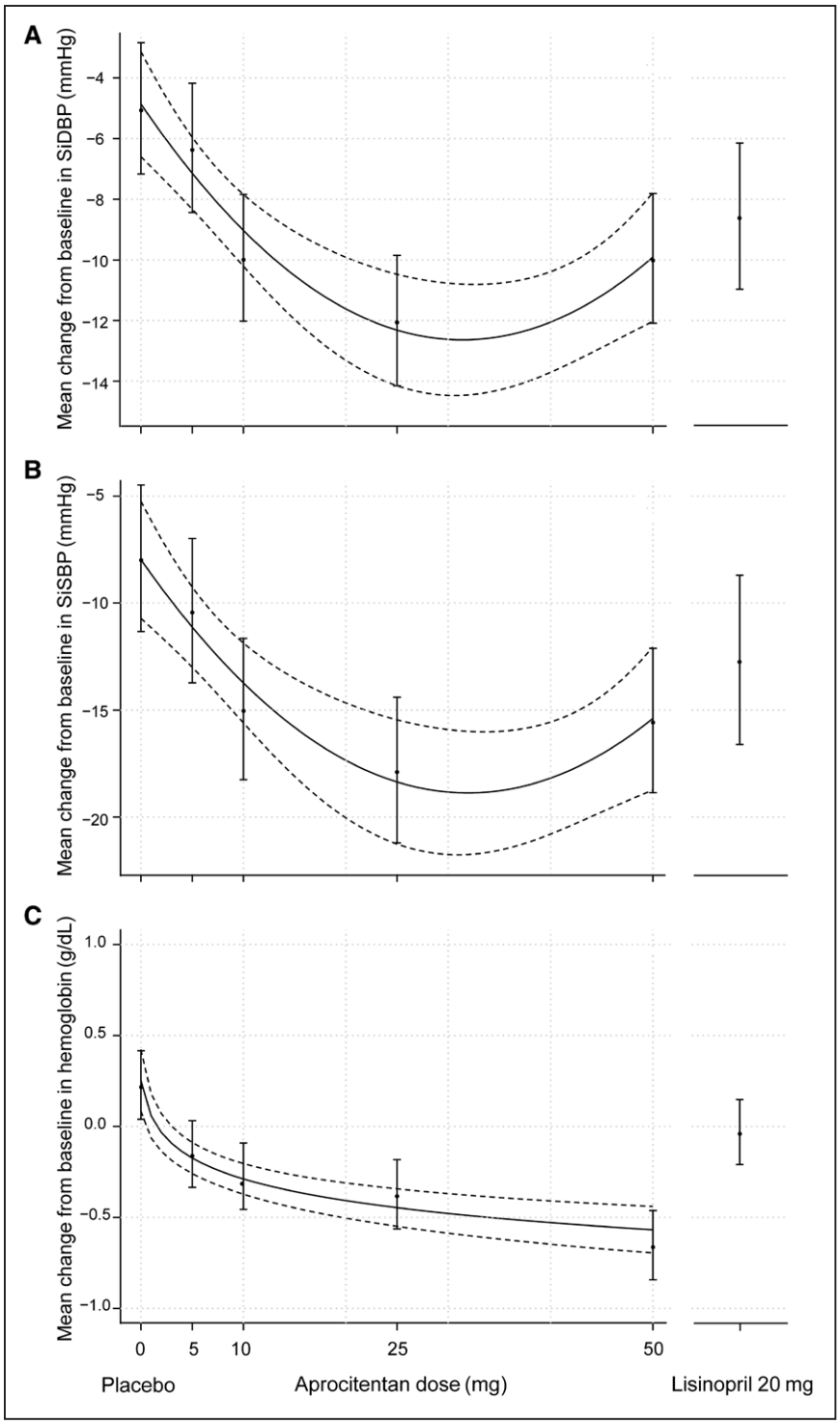

Figure 3. Results from multiple comparison procedure - modeling analysis. Change from baseline to week 8 in (**A**) sitting diastolic blood pressure (SiDBP) and (**B**) sitting systolic blood pressure (SiSBP)–quadratic model; (**C**) hemoglobin-linear in log dose model.

week 2. Changes were concurrent with the fall in BP and persisted until week 8.

It is important to distinguish between fluid retention due to increases in sodium versus hemodilution due to changes in PV. The absence of a change in body weight was not consistent with sodium and fluid retention. The small increase in PV of 5.1% to 6.9% observed with aprocitentan 10 to 25 mg, corresponding to a decrease in hemoglobin of 0.27 to 0.38 g/dL, can be produced by a minimal amount of vasodilation and volume redistribution.[36] These small changes may be unlikely to increase the risk of heart failure due to fluid retention.[10,11,35] Nevertheless, further investigation of aprocitentan in larger trials is warranted.

Dose Selection

As for any new antihypertensive drug, clinical development of aprocitentan requires the estimation of the minimum effective dose and maximum tolerated dose.[37,38] The maximum effect on BP was observed at 25 mg (difference versus placebo –9.90/–6.99 mm Hg), with an associated hemoglobin decrease of 0.38 g/dL and a PV increase of 6.9% (versus +0.22 g/dL and –0.3% with

Table 3. Change from Baseline to Week 8 in 24-Hour Mean Ambulatory BP (Per-Protocol Set Restricted to Patients With Valid Measurement at Baseline and Week 8, n=281)

		Aprocitentan				
	Placebo	5 mg	10 mg	25 mg	50 mg	Lisinopril
Ambulatory BP	n=44	n=49	n=47	n=47	n=51	n=43
24-h mean systolic BP, mm Hg						
Baseline	140.6 (14.5)	141.0 (15.3)	143.4 (16.7)	142.2 (13.6)	141.0 (15.1)	141.4 (15.9)
Change from baseline	–3.6	–2.8	–8.4	–8.9	–7.4	–7.2
	(8.1)	(9.8)	(11.2)	(10.2)	(9.1)	(15.4)
Placebo-corrected	…	0.87	–3.99	–4.83	–3.67	–3.43
95% CI*	…	–3.58 to 5.32	–8.49 to 0.52	–9.33 to –0.33	–8.08 to 0.73	–8.30 to 1.44
P value*		0.968	0.098	0.031	0.130	0.165
24-h mean diastolic BP, mm Hg						
Baseline	90.8	90.6	91.9	88.8	92.4	90.8
	(10.4)	(10.1)	(11.7)	(9.7)	(10.2)	(9.6)
Change from baseline	–2.5	–3.4	–6.9	–7.8	–7.4	–6.2
	(6.6)	(6.2)	(7.1)	(7.9)	(6.4)	(9.9)
Placebo-corrected	…	–0.97	–4.04	–5.89	–4.45	–3.66
95% CI*	…	–4.09 to 2.16	–7.20 to –0.88	–9.05 to –2.72	–7.56 to –1.35	–6.96 to –0.36
P value*		0.859	0.007	<0.001	0.002	0.030

Values are means (SD) unless otherwise stated. BP indicates blood pressure.
*Dunnett correction for testing multiple aprocitentan doses vs placebo.

placebo). Aprocitentan 50 mg did not decrease BP further but increased the effects on hemoglobin (–0.67 g/dL) and PV (9.5%). Although we do not have a maximum tolerated dose, there are signs that we may have effect on fluid retention with 50 mg. A dose of 10 mg provided 50% of the maximum effect, with a hemoglobin decrease of 0.27 g/dL and PV increase of 5.1%. Based on our data, we estimated that the minimum clinically effective dose is approximately 10 mg. Doses between 10 and 25 mg should be investigated further for the treatment of hypertension.

Other Findings

One interesting observation was the dose-dependent effect of aprocitentan on serum urate levels. In the absence of hyponatremia and sign of excess antidiuretic hormone, the most likely explanation for the reduction in serum urate levels was a reduction in renal proximal tubule reabsorption of urate due to an increase in the effective renal circulating volume linked to ET blockade. A similar effect on urate excretion has been reported with other ERAs.

Limitations

Although the monotherapy setting may seem a limitation of the study, the effects of antihypertensives targeting different pathways are expected to be additive, meaning dose selection can be performed independently of the setting. The fact that aprocitentan-like and lisinopril-like capsules are similar but not the same may be another study limitation, although it is unlikely that investigators were able to identify one group (aprocitentan 10 mg) as being different from the others.

Perspectives

By targeting the ET system, aprocitentan may offer a new therapeutic option for patients with difficult-to-control hypertension. In the present study, monotherapy with aprocitentan produced a clinically relevant reduction in BP in untreated patients with mild-to-moderate hypertension without causing any serious AEs.

The potential benefits of aprocitentan in combination with other agents to treat patients with difficult-to-control (ie, resistant) hypertension is currently being investigated (https://www.clinicaltrials.gov; Unique identifier: NCT03541174).

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Disclosures

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Novelty and Significance

What Is New?

- This is the first clinical trial conducted with the dual endothelin receptor antagonist aprocitentan in patients with essential hypertension. Two novel aspects of this study were the use of unattended automated office blood pressure (BP) in a dose-response hypertension study and the use of Multiple Comparison Procedure–Modeling to model the dose-response relationship.

What Is Relevant?

- This study demonstrated that monotherapy with aprocitentan reduces BP in a dose-dependent manner without producing serious adverse effects with limited but dose-dependent variation in plasma volume. Aprocitentan doses of 12.5 and 25 mg were selected for further clinical development.

Summary

Aprocitentan, a dual endothelin receptor antagonist, was evaluated in a dose-response study examining its effects on BP in 490 patients with mild-to-moderate hypertension. Changes in BP were evaluated using unattended automated office BP and 24-hour ambulatory BP monitoring. Significant decreases in BP were noted at doses of 10, 25, and 50 mg once daily with the optimum antihypertensive dose being 10 to 25 mg. Aprocitentan was well tolerated in each treatment group.