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ORIGINAL ARTICLE



Aprocitentan in Patients With Chronic Kidney Disease and Resistant Hypertension

Patrick Rossignol¹, Martine Clozel, Roland F. Dreier, John M. Flack², Bruno Flamion³, Johannes Mann, Krzysztof Narkiewicz, Mouna Sassi-Sayadi, Ji-Guang Wang⁴, Michael Weber⁵, Markus Schlaich⁶

BACKGROUND: Hypertension is a cause and consequence of chronic kidney disease (CKD). Resistant hypertension is common and often difficult to control in patients with CKD. This post hoc analysis evaluated the efficacy and safety of aprocitentan (with standardized background antihypertensive therapy) in patients with CKD and resistant hypertension, a group with high morbidity and mortality risk and limited treatment options.

METHODS: The PRECISION study (Parallel-Group, Phase 3 Study With Aprocitentan in Subjects With Resistant Hypertension) consisted of part 1: 4-week, double-blind (aprocitentan 12.5 and 25 mg versus placebo); part 2: 32-week, single-blind (aprocitentan 25 mg); and part 3: 12-week, double-blind withdrawal (aprocitentan 25 mg versus placebo). In participants with CKD, aprocitentan's effect on blood pressure (BP), urine albumin-to-creatinine ratio, and safety was evaluated.

RESULTS: Of 730 participants in PRECISION, 147 had CKD categorized as KDIGO high risk or very high risk. At week 4, aprocitentan 12.5 mg, aprocitentan 25 mg, and placebo reduced office systolic BP by -13.5 , -16.6 , and -4.4 mmHg, respectively; this was maintained with aprocitentan 25 mg to week 36 (-16.4 mmHg). At week 4, reductions in nighttime ambulatory systolic BP were -9.6 , -13.8 , and -2.5 mmHg, respectively. Changes in urine albumin-to-creatinine ratio were -47.1% , -59.6% , and -2.4% , respectively, maintained with aprocitentan 25 mg to week 36 (-61.6%). Aprocitentan was generally well tolerated (no change in potassium or estimated glomerular filtration rate); early peripheral edema was the most common adverse event.

CONCLUSIONS: Aprocitentan was well tolerated; efficiently lowered BP, particularly nighttime ambulatory BP; and markedly reduced urine albumin-to-creatinine ratio in participants with CKD and resistant hypertension. Aprocitentan may confer considerable cardiovascular and kidney-protective benefits in these difficult-to-treat patients.

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Key Words: antihypertensive agents ■ blood pressure ■ calcium channel blockers ■ cardiovascular diseases ■ renal insufficiency, chronic

Hypertension is both a cause and a consequence of chronic kidney disease (CKD). In patients with CKD, hypertension is highly prevalent (60%–90%)^{1–3} and more difficult to control than in the non-CKD population.^{4–6} A complex interplay of multiple factors contributes to both conditions, including an upregulated

renin-angiotensin-aldosterone system, increased sympathetic nerve activity, vascular remodeling, and endothelial dysfunction.^{6,7}

Resistant hypertension (RHT) is a term used if blood pressure (BP) remains uncontrolled despite treatment with maximally tolerated doses of at least 3

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NOVELTY AND RELEVANCE

What Is New?

This is the first report on aprocitentan, a drug targeting the endothelin pathway, in patients with chronic kidney disease and resistant hypertension, a group of difficult-to-treat patients with a high risk of morbidity and mortality and limited treatment options.

What Is Relevant?

Before initiation of aprocitentan, the blood pressure of patients remained uncontrolled despite receiving ≥ 3 antihypertensive drugs, including an angiotensin receptor blocker targeting the traditional

renin-angiotensin-aldosterone pathway. Aprocitentan (plus ≥ 3 antihypertensive drugs) achieved clinically meaningful, substantial reductions in office and ambulatory blood pressure, and urine albumin-to-creatinine ratio in these high-risk patients.

Clinical/Pathophysiological Implications?

Targeting the endothelin pathway, aprocitentan showed considerable cardiovascular and kidney-protective benefits, suggesting that add-on therapy with aprocitentan could lead to long-term health benefits in patients with chronic kidney disease and resistant hypertension.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CKD	chronic kidney disease
DBP	diastolic blood pressure
DB-WD	double-blind withdrawal
eGFR	estimated glomerular filtration rate
ERA	endothelin receptor antagonist
ET	endothelin
ET_A	endothelin A
ET_B	endothelin B
KDIGO	Kidney Disease Improving Global Outcomes
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PRECISION	Parallel-Group, Phase 3 Study With Aprocitentan in Subjects With Resistant Hypertension
RHT	resistant hypertension
SBAT	standardized background antihypertensive therapy
SBP	systolic blood pressure
SiDBP	sitting office diastolic blood pressure at trough
SiSBP	sitting office systolic blood pressure at trough
UACR	urine albumin-to-creatinine ratio

antihypertensive medications from different classes, including a diuretic.^{1,8} RHT occurs more often among patients with CKD than in the non-CKD population.^{4,9} Inversely, CKD is one of the most common comorbidities observed in patients with RHT.⁴

In patients with CKD, hypertension significantly contributes to preventable morbidity and mortality and is a leading cause of cardiovascular disease.^{4,5,10} In 2019, there were >650 million people with CKD worldwide and 1.2 million deaths due to CKD.¹¹ Especially, nocturnal hypertension has been associated with increased cardiovascular morbidity.^{12–14} Therefore, appropriate and effective management of hypertension is a key strategy of managing these patients.^{8,15}

In patients with CKD and hypertension, recent guidelines recommend treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, calcium channel blockers, and diuretics to achieve office systolic BPs (SBPs) <130 mmHg (American guidelines), <120 to 139 mmHg (European guidelines), and <120 mmHg (Kidney Disease Improving Global Outcomes [KDIGO] guidelines).^{8,15–17} KDIGO also recommends a mineralocorticoid receptor antagonist (MRA) for the treatment of RHT in patients with CKD.¹⁵ However, the long-term effects of steroidal MRAs are unknown in these patients.^{1,15}

The ET (endothelin) pathway is frequently activated in patients prone to developing RHT, including those with CKD.^{4,7} Upregulation of ET-1 is considered an important contributor to the pathophysiology of CKD progression, including increased BP, glomerular membrane permeability, mesangial cell proliferation, podocyte dysfunction, interstitial inflammation, and fibrosis.^{18,19} Targeting the ET pathway has emerged as a novel approach in the management of hypertension and may confer kidney-protective effects.^{20–23} ET receptor antagonists (ERAs) are approved for the treatment of Immunoglobulin A nephropathy and investigated for the treatment of CKD,^{18,23} but there are no studies assessing ERAs for the treatment of RHT in patients with CKD.

Aprocitentan,²⁴ a dual ET_A (ET A)/ET_B (ET B) receptor antagonist, assessed in patients with confirmed RHT in PRECISION (Parallel-Group, Phase 3 Study With

Aprocitentan in Subjects With Resistant Hypertension),²⁵ is indicated for the treatment of hypertension in combination with other antihypertensives, in adults not adequately controlled on other drugs.^{26,27} The latest American College of Cardiology/American Heart Association guidelines also recommend aprocitentan as an add-on therapy for these patients.¹⁷ The efficacy, tolerability, and safety of aprocitentan in patients with CKD and RHT have not been described in detail up to now.

This post hoc analysis of patients with RHT enrolled in PRECISION assessed the efficacy and safety of aprocitentan (in addition to standardized background antihypertensive therapy [SBAT]) in subgroups with RHT and kidney impairment. Subgroups were defined according to criteria commonly used in the literature and overlapped to some extent: (1) participants with CKD who are categorized as high risk or very high risk based on KDIGO criteria¹⁵ (termed KDIGO \geq high risk hereafter; focus of our analysis), (2) participants with CKD stage 3a/b or 4, and (3) participants with microalbuminuria or macroalbuminuria.

METHODS

Data Availability

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

Study Design

The phase 3 PRECISION trial investigated the efficacy and safety of aprocitentan 12.5 and 25 mg in participants with confirmed RHT.²⁵ The study design has been described previously (Figure S1).^{25,28} Eligibility criteria included a sitting office SBP at trough (SiSBP) \geq 140 mm Hg (unattended automated office BP measured at trough), an estimated glomerular filtration rate (eGFR) \geq 15 mL/min per 1.73 m², and NT-proBNP (N-terminal pro-B-type natriuretic peptide) $<$ 500 pg/mL.^{25,28}

During screening, participants were switched from their existing antihypertensive medications (except β -blockers) to fixed-dose, triple-combination SBAT, consisting of amlodipine 5 or 10 mg, valsartan 160 mg, and hydrochlorothiazide 25 mg, which was maintained throughout the study. Participants on other diuretics at screening, including loop diuretics, had to stop these drugs and switch to hydrochlorothiazide as part of SBAT. Adherence to SBAT was \approx 98% for the overall study population during the entire study.²⁹

The active treatment phase of PRECISION consisted of 3 parts: part 1: double-blind aprocitentan 12.5 mg, aprocitentan 25 mg, or placebo to week 4; part 2: single-blind aprocitentan 25 mg to week 36; part 3: double-blind withdrawal (DB-WD) to week 48, after rerandomization at week 36 (withdrawal baseline) to placebo or aprocitentan 25 mg. A 30-day safety follow-up period completed the study (Figure S1).

Subgroups of Participants With Kidney Impairment

Participants categorized as KDIGO \geq high risk¹⁵ included participants with eGFR \geq 15 to $<$ 45 mL/min per 1.73m², eGFR \geq 45

to $<$ 60 mL/min per 1.73 m² and urine albumin-to-creatinine ratio (UACR) \geq 30 mg/g, and eGFR \geq 60 mL/min per 1.73 m² and UACR $>$ 300 mg/g. Participants were also categorized by CKD stages 3 and 4 (CKD stage 3a/b: eGFR =30– $<$ 60 mL/min per 1.73 m²; CKD stage 4: eGFR =15– $<$ 30 mL/min per 1.73 m²) and by albuminuria levels at baseline (normal: UACR $<$ 30 mg/g; microalbuminuria: UACR =30–300 mg/g; and macroalbuminuria: UACR $>$ 300 mg/g). Differences in the composition of the subgroups with kidney impairment are illustrated in Figure S2.

Efficacy End Points

The mean change from baseline or withdrawal baseline in unattended SiSBP and sitting office diastolic BP at trough (SiDBP) over time, the mean change from baseline to week 4 and from withdrawal baseline to week 40 in daytime and nighttime ambulatory SBP and diastolic DP (DBP), and the percentage change in UACR (measured on spot urine samples at trough) from baseline or withdrawal baseline over time were assessed. Changes in eGFR were measured from baseline to weeks 4 and 36 and from the withdrawal baseline to weeks 40 and 48 (acute changes) and between weeks 6 and 36 when all participants received 25 mg aprocitentan (chronic slope).³⁰

The correlation between changes in SiSBP and UACR was assessed at weeks 4 and 36 (Figure S3). The correlation coefficient R, a value between -1 and 1 , measures the strength of the linear relationship between the 2 quantitative variables, namely, SiSBP and UACR in our analysis. A value of R close to 1 would indicate a strong positive correlation.

Safety End Points

Safety outcomes included all treatment-emergent adverse events, defined using the Medical Dictionary for Regulatory Dictionaries (version 24.1). Bodyweight and laboratory measurements, including serum NT-proBNP, potassium, sodium, and hemoglobin, were assessed at baseline, weeks 4 and 36, withdrawal baseline, and weeks 40 and 48. Percent changes in estimated plasma volume were assessed by the Strauss formula, between baseline and week 4, and weeks 36 and 40.^{31,32}

Statistical Analysis

SiSBP, SiDBP, and UACR (log transformed) were analyzed using a mixed model with factors for treatment group, visit, and treatment by visit interaction, covariates for baseline or withdrawal baseline SBP/DBP (or log UACR), and the interaction between baseline or withdrawal baseline and visit (for further details, see the study by Schlaich et al²⁵ and the study by Danaietash et al²⁸). Ambulatory SBP and DBP were assessed by ANCOVA with a factor for treatment group and a covariate for baseline (or withdrawal baseline) 24-hour mean SBP/DBP. Descriptive statistics are reported as means (SD) or mean (SE), or geometric mean ratio/ mean percent change (95% CI) for quantitative variables. Frequencies and percentages were used for qualitative data. For the generation of the Forest plots, the mixed model for the main analyses (SiSBP, daytime/nighttime SBP, and UACR) was extended with factors for the subgroup and treatment by subgroup interaction. Placebo-corrected least square means with 95% CIs were used for inference

without multiplicity adjustment. All analyses were post hoc and exploratory.

RESULTS

Participants With KDIGO \geq High Risk

Of the 730 participants with RHT enrolled in PRECISION, 147 (20.1%) were categorized as KDIGO \geq high risk (Figure S4). Compared with the non-high-risk KDIGO group ($n=583$), participants with KDIGO \geq high risk were older (66.1 versus 60.6 years), more likely to be male (70.7% versus 56.6%), and Black (17.0% versus 9.8%), on ≥ 4 antihypertensive medications (71.4% versus 60.9%), including β -blockers (72.8% versus 59.9%), and were taken off loop diuretics at screening (20.4% versus 13.2%; Table S1). The KDIGO \geq high risk and the non-high-risk KDIGO groups differed in comorbidities at baseline, including diabetes (79.6% versus 47.7%), congestive heart failure (12.9% versus 21.3%), and sleep apnea syndrome (20.4% versus 12.5%; Table S1). Mean baseline BPs (SiSBP, SiDBP, and ambulatory SBP and DBP) were similar in both KDIGO groups (Table S1).

Participants with KDIGO \geq high risk were equally distributed across the treatment arms (49, 52, and 46 participants received aprocitentan 12.5 mg, aprocitentan 25 mg, and placebo, respectively), and baseline demographics, disease characteristics, and medical history were well balanced (Table S1).

Efficacy of Aprocitentan in Participants With KDIGO \geq High Risk

Aprocitentan 12.5 and 25 mg in addition to SBAT lowered SiSBP and SiDBP in participants with KDIGO \geq high risk. From baseline to week 4 (part 1), aprocitentan 12.5 and 25 mg reduced mean SiSBP (SE) by -13.5 (2.3) and -16.6 (1.9) mmHg, respectively, compared with -4.4 (2.9) mmHg with placebo (Figure 1). At week 36, the reduction in SiSBP was -16.4 (1.9) mmHg versus baseline. From the DB-WD baseline at weeks 36 to 40, SiSBP increased by 5.5 (2.7) mmHg in participants rerandomized to placebo compared with -0.8 (2.0) mmHg in participants continuing aprocitentan 25 mg (Figure 1). Similar changes over time were observed when assessing SiDBP (Figure S5A).

Aprocitentan 12.5 and 25 mg lowered daytime and nighttime ambulatory SBP (Figure 2). During part 1, aprocitentan 12.5 and 25 mg reduced mean daytime ambulatory SBP (SE) by -8.5 (2.2) and -7.9 (2.6) mmHg, respectively, compared with 2.7 (3.1) mmHg with placebo. Nighttime ambulatory SBP reductions were even more pronounced with -9.6 (2.1), -13.8 (2.8), and -2.5 (3.1) mmHg, respectively. From the DB-WD baseline to week 40, daytime SBP remained similar for placebo (1.4 [1.9] mmHg) and aprocitentan 25 mg (-2.3 [2.5] mmHg), while nighttime

SBP increased with placebo (10.3 [2.2] mmHg) but not with aprocitentan 25 mg (0.0 [2.0] mmHg; Figure 2). Similar changes were observed when assessing daytime and nighttime ambulatory DBPs (Figure S5B).

Aprocitentan markedly reduced UACR. During part 1, the mean percentage change in UACR (95% CI) with aprocitentan 12.5 and 25 mg was -47.1% (-56.1 to -36.4) and -59.6% (-69.1 to -47.1), respectively, compared with -2.4% (-24.4 to 26.1) with placebo (Figure 3). At week 36, the percentage change in UACR was -61.6% (-70.2 to -50.7 ; Figure 3). During part 3, UACR doubled within 4 weeks in participants rerandomized to placebo (108.3% [46.0–197.1]), whereas UACR decreased further in those continuing aprocitentan 25 mg (-12.9% [-26.1 to 2.7]; Figure 3).

The correlation coefficients for changes in SiSBP versus changes in UACR from baseline to week 4 across the 3 treatment groups (R range, 0.12–0.32) and from baseline to week 36 for aprocitentan 25 mg ($R=0.29$) were all considerably >1 (Figure S3).

Baseline eGFR was 48.3 to 50.7 mL/min per 1.73 m^2 across the treatment arms in participants with KDIGO \geq high risk. Changes in mean eGFR (SD) from baseline to week 4 were 0.5 (8.1), -2.5 (8.4), and -0.4 (8.2) mL/min per 1.73 m^2 with aprocitentan 12.5 mg, aprocitentan 25 mg, and placebo, respectively (Table S2). In part 3, there were minimal changes in mean eGFR from the DB-WD baseline to week 48 with aprocitentan 25 mg and placebo (-1.0 [9.4] and -1.1 [9.1] mL/min per 1.73 m^2 , respectively; Table S2). From weeks 6 to 36 (aprocitentan 25 mg), the least square mean (95% CI) of the chronic eGFR slope was -0.9 (-4.0 to 2.2) mL/min per 1.73 m^2/y .

Efficacy Outcomes in Other Subgroups With Kidney Impairment

The efficacy of aprocitentan (12.5 and 25 mg) on BP and UACR was similar across all subgroups with kidney impairment (KDIGO \geq high risk, CKD stages 3 or 4, or microalbuminuria or macroalbuminuria; Figures 1–3, Figures S5–S8, and Tables S3 and S4 list baseline demographics and disease characteristics for participants with CKD stages 3 and 4, and microalbuminuria and macroalbuminuria, respectively). In participants with macroalbuminuria, aprocitentan had the most pronounced effect in lowering mean UACR (95% CI): up to -63% (-72 to -53) with aprocitentan 25 mg during part 1 and -67% (-75 to -55) during part 2 (Figure S7B). Aprocitentan had similar or greater efficacy in participants with kidney impairment compared with the overall phase 3 population (Figure 4).

Safety Outcomes in Participants With KDIGO \geq High Risk

Aprocitentan was well tolerated in participants with KDIGO \geq high risk (Table S5). Edema was the most

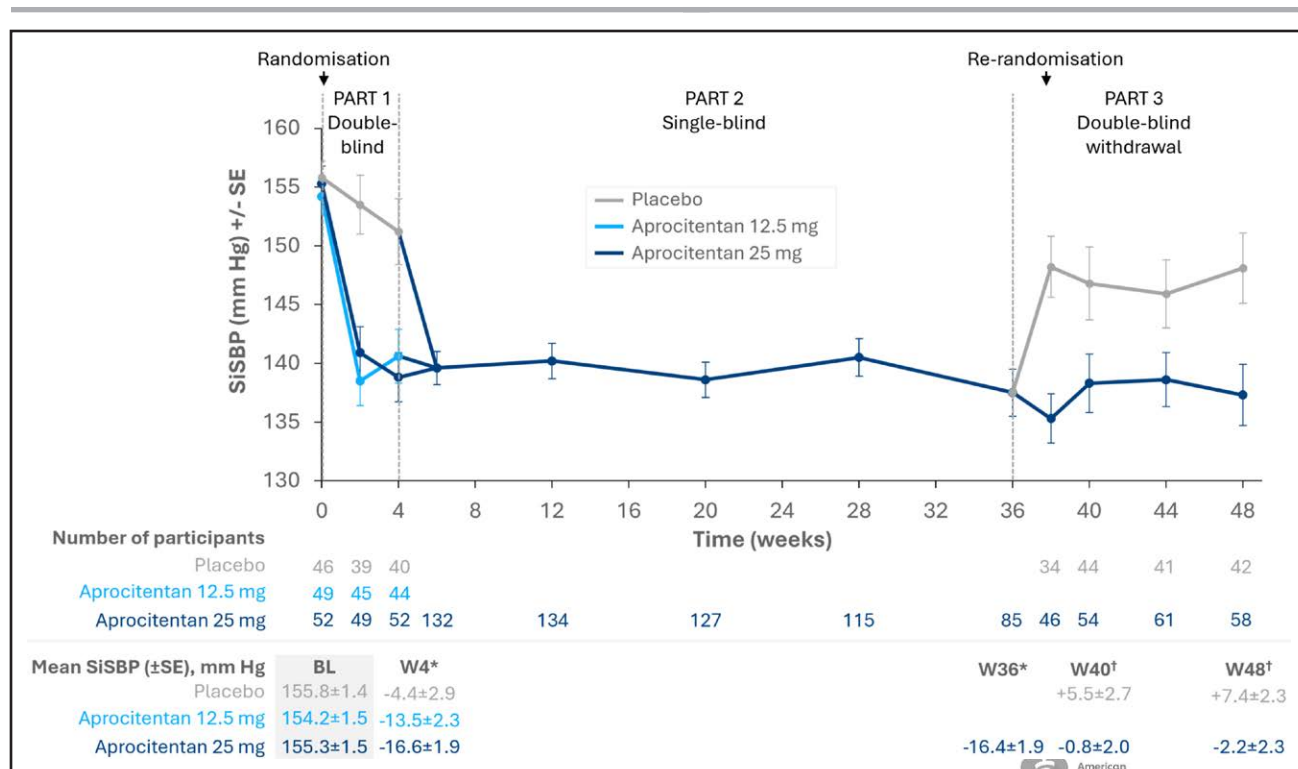


Figure 1. Efficacy of aprocitentan on unattended office systolic blood pressure at trough (SiSBP) over time in participants with Kidney Disease Improving Global Outcomes (KDIGO) ≥high risk and resistant hypertension.

Mean SiSBP over time with aprocitentan 12.5 mg, aprocitentan 25 mg, and placebo was measured at trough as unattended automated office blood pressure before treatment administration (study treatment and the standardized background antihypertensive therapy). Error bars are SEM. The subgroup KDIGO ≥high risk includes participants enrolled in PRECISION (Parallel-Group, Phase 3 Study With Aprocitentan in Subjects With Resistant Hypertension) categorized as high risk or very high risk based on the KDIGO criteria.¹⁵ Please refer to Figure S1 for details on the 3-part study design of PRECISION. *Mean change (±SE) from baseline (BL), mmHg. †Mean change (±SE) from the double-blind withdrawal (DB-WD) BL at week 36, mmHg; mean SiSBP at the DB-WD BL was 140.0±2.7 mmHg in participants rerandomized to placebo (n=46) and 139.6±2.3 mmHg in participants continuing aprocitentan 25 mg (n=64).

common adverse event with aprocitentan; almost all edema events were mild or moderate peripheral leg edema. They were effectively managed with or without additional diuretic therapy (Table S6). Three participants (2.1%) discontinued due to edema during 48 weeks of the study (there were no discontinuations during PRECISION in participants randomized to aprocitentan 12.5 mg in part 1). Of participants with KDIGO ≥high risk who received aprocitentan (any dose) at any time during PRECISION (N=145), 37.9% (n=55) had at least 1 edema event during the study (Table S6). This compares with 25.4% (n=184 of 724) in the overall phase 3 population. The incidence of new or recurrent edema events measured in 4-week time intervals was 2.0% before randomization and 16.3% and 15.1% with aprocitentan 12.5 and 25 mg, respectively, versus 4.4% with placebo up to week 4 (placebo not shown; Figure S9). By weeks 12 to 16 (all participants receiving aprocitentan 25 mg), incidence rates returned to prerandomization rates and remained low for the remainder of the trial. Of participants with KDIGO ≥high risk who received aprocitentan (any dose) at any time during PRECISION, 29% (n=42 of

145) were switched from loop diuretics or >1 diuretic to hydrochlorothiazide as part of SBAT before randomization. The incidence of edema was higher among those participants who were switched from a more potent diuretic treatment to hydrochlorothiazide (55%; n=23 of 42; Table S6) compared with 31% (n=32 of 103) among those who did not decrease their diuretics before randomization.

Eleven participants had heart failure events: none were considered to be related to study treatment, and none led to discontinuation of the study. Of the 11 participants with heart failure events, 7 required hospitalization (part 1: n=2 receiving aprocitentan 25 mg; part 2: n=4; follow-up to part 3: n=1 receiving placebo [15 weeks after switching from aprocitentan]). Besides KDIGO ≥high risk, these 7 participants had additional risk factors for heart failure, including a medical history of diabetes (all n=7) and a medical history of heart failure (n=3). Of the 4 participants without a medical history of heart failure, 2 had elevated NT-proBNP levels at screening (385 and 1124 pg/mL, respectively). All 7 participants received β-blockers.²⁸ Four of the 7 participants were switched from a more potent diuretic at screening to

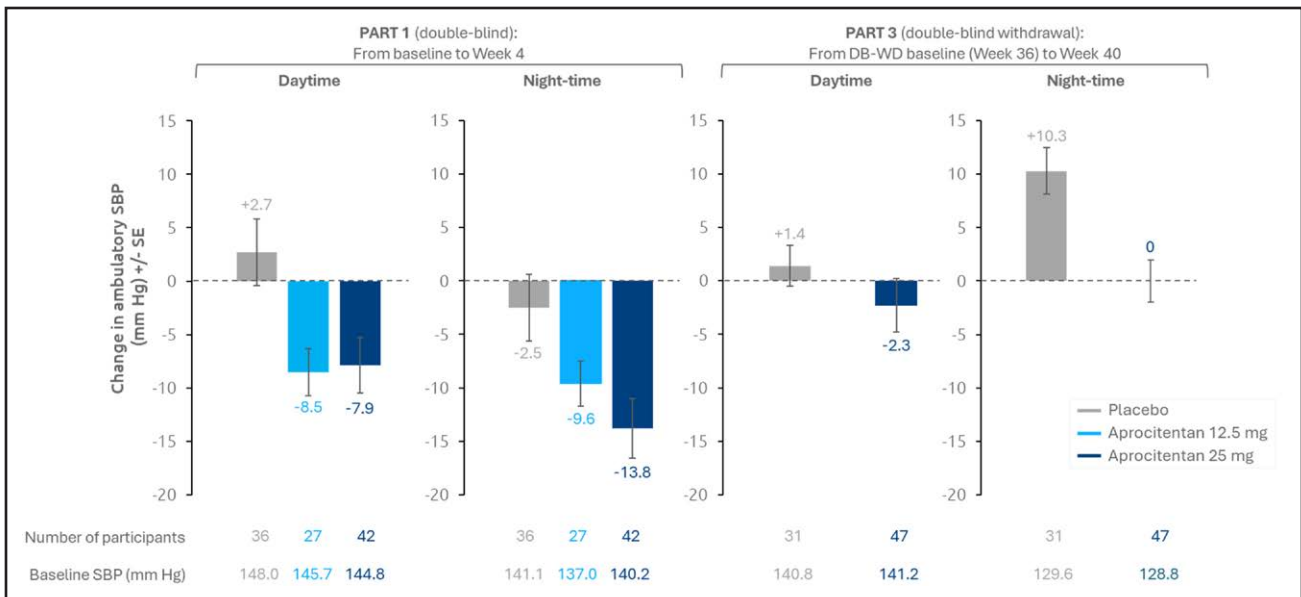


Figure 2. Efficacy of aprocitentan on daytime and nighttime systolic blood pressure (SBP) in participants with Kidney Disease Improving Global Outcomes (KDIGO) \geq high risk and resistant hypertension.

Mean change in daytime and nighttime ambulatory SBP from baseline (BL) to week 4 and from the double-blind withdrawal (DB-WD) BL (week 36) to week 40 with aprocitentan 12.5 mg, aprocitentan 25 mg, and placebo was measured by 24-hour ambulatory blood pressure monitoring after treatment administration (study treatment and the standardized background antihypertensive therapy). Bars are SEM. The subgroup KDIGO \geq high risk includes participants enrolled in PRECISION (Parallel-Group, Phase 3 Study With Aprocitentan in Subjects With Resistant Hypertension) categorized as high risk or very high risk based on the KDIGO criteria.¹⁵ Please refer to Figure S1 for details on the 3-part study design of PRECISION.

hydrochlorothiazide as part of SBAT. All 7 responded to treatment with loop diuretics and cases resolved.

There were no excess headaches, no orthostatic hypotension, and no tachycardia. No acute kidney injuries (defined based on the study by Kellum and Lameire³³) occurred during PRECISION.

Potassium and sodium levels were stable throughout the study (Tables S7 and S8).

Baseline NT-proBNP levels ranged from 15.4 to 20.6 pmol/L across the treatment arms. NT-proBNP remained unchanged with aprocitentan 12.5 mg, increased by 10% with aprocitentan 25 mg, and decreased by 10% with placebo during part 1 (geometric mean ratio [95% CI] from baseline to week 4: aprocitentan 12.5 mg: 1.0 [0.8–1.2]; aprocitentan 25 mg: 1.1 [0.9–1.2]; and placebo: 0.9 [0.7–1.1]). NT-proBNP levels were \approx 20% higher than baseline at week 36 (aprocitentan 25 mg: 1.2 [1.0–1.4]). From DB-WD baseline to week 40, NT-proBNP levels remained stable with aprocitentan 25 mg (1.0 [0.9–1.1]) and placebo (0.9 [0.8–1.1]; Table S9).

Hemoglobin concentrations ranged from 131.0 to 132.0 g/L at baseline (Table S10). Levels decreased by \approx 8% with aprocitentan 12.5 and 25 mg during part 1 (baseline to week 4; mean [SD]: -10.2 [8.9] and -10.3 [6.8] g/L, respectively, versus -2.0 [7.1] g/L with placebo), stabilized during part 2 (baseline to week 36: -11.8 [8.6] g/L) and reversed upon withdrawal (weeks 36–40: aprocitentan 25 mg: 0.0 [6.3] g/L; placebo: 9.2 [10.0] g/L; Table S10). Mean percentage changes in

estimated plasma volume (SE) during part 1 were 14.6% (2.0) and 13.7% (1.4) with aprocitentan 12.5 and 25 mg, respectively (versus 3.2% [1.5] with placebo), and reversed upon withdrawal (aprocitentan 25 mg: 0.9% [1.2]; placebo: -9.6% [1.4]; Table S11).

The mean bodyweight at baseline ranged from 94.0 to 98.2 kg (Table S12). Transient minimal increases in mean bodyweight (SD) with aprocitentan 12.5 and 25 mg during part 1 (0.7 [1.5] and 0.6 [1.7] kg, respectively, versus -0.1 [1.8] kg with placebo), reversed with aprocitentan 25 mg during part 2 (-1.0 [3.3] kg). In part 3, the mean bodyweight decreased with aprocitentan 25 mg by -0.5 (2.1) kg and with placebo by -1.2 (1.6) kg from the DB-WD baseline to week 40 (Table S12).

DISCUSSION

This post hoc analysis of PRECISION in subgroups with kidney impairment and RHT showed that aprocitentan (in addition to triple-combination SBAT of amlodipine, valsartan, and hydrochlorothiazide; with or without β -blockers) was generally well tolerated (with edema being the most common adverse event) and efficiently lowered office and ambulatory SBP and DBP, with the effect on nighttime ambulatory SBP and DBP being especially pronounced. Aprocitentan also markedly reduced UACR (up to -67%) without reducing eGFR. The analysis focused on participants categorized as KDIGO \geq high risk with confirmatory results in participants with CKD

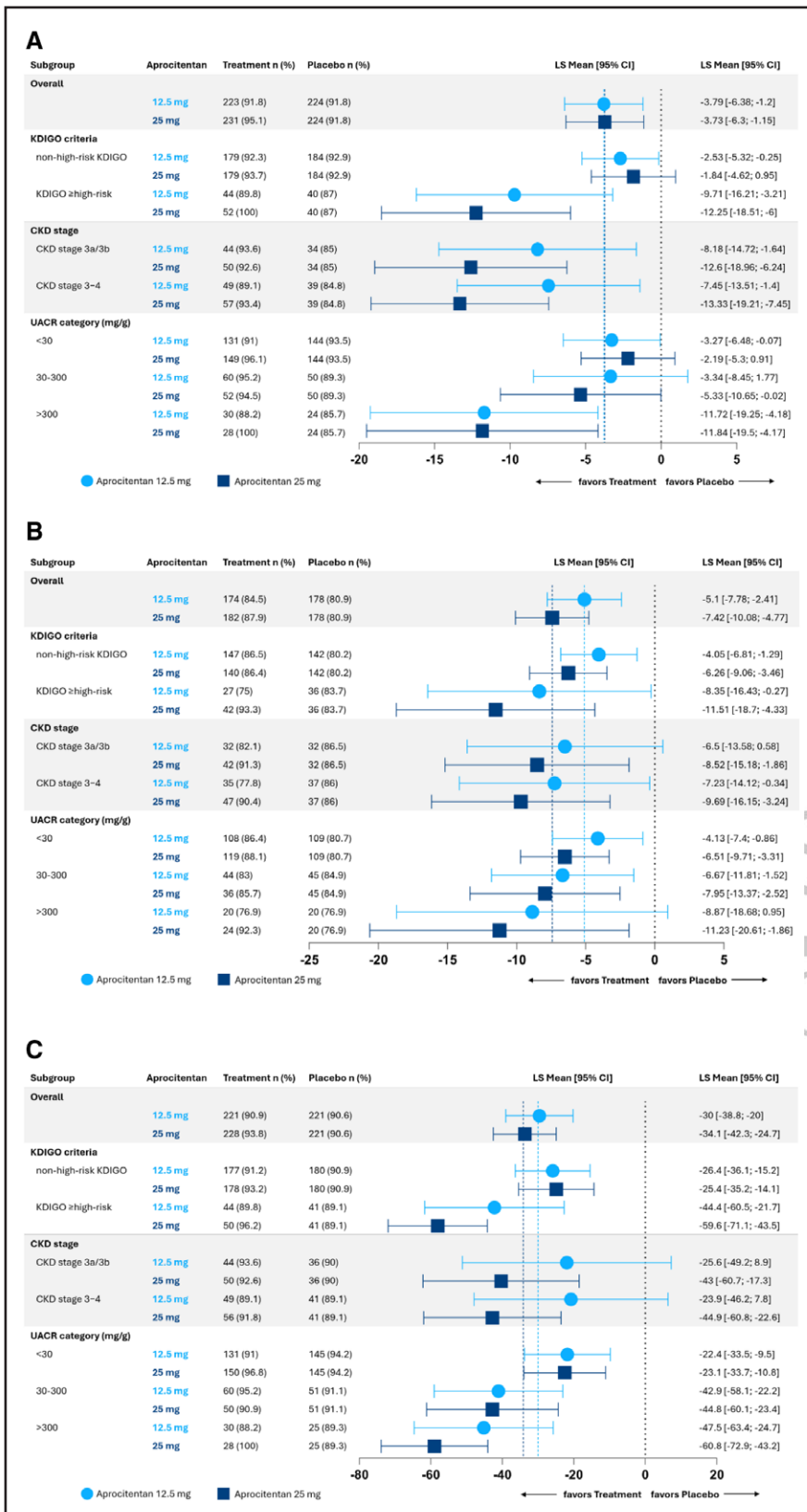


Figure 4. Subgroup analyses for change from baseline to week 4 in sitting systolic blood pressure (SiSBP), nighttime systolic blood pressure (SBP), and urine albumin-to-creatinine ratio (UACR) in subgroups with kidney impairment and resistant hypertension.

Forest plots of the placebo-corrected least square (LS) mean (95% CI) change in SiSBP (A), change in nighttime ambulatory SBP (B), and percentage change in UACR (C) from baseline to week 4 with aprocitentan 12.5 mg and aprocitentan 25 mg. SiSBP (mmHg) was measured at trough as unattended automated office blood pressure before treatment administration (study treatment and the standardized background antihypertensive therapy). Nighttime SBP (mmHg) was measured by 24-hour ambulatory blood pressure monitoring after treatment administration. UACR (% change) was measured on spot urine samples on the morning after treatment administration. The geometric ratio of UACR was transformed to a percentage change $[(\text{ratio}-1)] \times 100$. The Kidney Disease Improving Global Outcomes (KDIGO) \geq high risk subgroup includes participants enrolled in PRECISION (Parallel-Group, Phase 3 Study With Aprocitentan in Subjects With Resistant Hypertension) and categorized as high risk or very high risk based on the KDIGO criteria.¹⁵ Chronic kidney disease (CKD) stage 3a/b is defined as estimated glomerular filtration rate (eGFR) =30 to <60 mL/min per 1.73 m², and CKD stages 3 and 4 are defined as eGFR=15 to <60 mL/min per 1.73 m². Subgroups defined by albumin levels at baseline include normal albumin levels (UACR<30 mg/g), microalbuminuria (UACR=30–300 mg/g), and macroalbuminuria (UACR>300 mg/g). Colored dashed vertical lines indicate the LS mean of the overall study population for aprocitentan 12.5 mg (light blue) and aprocitentan 25 mg (dark blue) as reference; the gray dashed vertical line indicates the effect threshold.

surrogate for slowing CKD progression.⁴⁷ Aprocitentan had a marked antiproteinuric effect in all subgroups with kidney impairment, reducing UACR up to -63% at

week 4 and up to -67% at week 36. These reductions in UACR without changes in eGFR suggest a robust kidney-protective effect of aprocitentan.

The correlation analyses show that the significant reductions in BP with aprocitentan do not solely explain the observed reductions in UACR, suggesting that additional mechanisms are involved in aprocitentan's kidney-protective effect, such as a decrease in glomerular permeability, postglomerular vasodilation, or functional tubular changes.⁴⁸

Aprocitentan was generally well tolerated in participants with CKD and RHT. The safety data of our study are in line with those of the phase 3 PRECISION study²⁵ without any additional safety signals. The most frequent adverse event with aprocitentan in the KDIGO \geq high-risk group was edema, with almost all events being of mild or moderate severity and the most common event being peripheral (leg) edema. Edema events were clinically manageable with additional diuretic therapy and lowering the dose of amlodipine. Edema events are a known side effect of ERAs.⁴⁹ In addition, CKD is a risk factor for edema: compared with the general population, patients with kidney dysfunction are more prone to edema events due to their tendency to retain sodium and fluid with advancing kidney disease.⁴⁹ Accordingly, a higher proportion of participants with KDIGO \geq high risk had edema events compared with the overall phase 3 population (37.9% versus 25.4%) during the 48 weeks of PRECISION. Importantly, after a transient increase in the risk of edema postrandomization to aprocitentan, the incidence of edema events returned to prerandomization rates (after \approx week 12) and remained low until study completion.

As part of the PRECISION study design, 8 weeks before randomization, participants were taken off their existing antihypertension medication, including diuretics, and switched to SBAT, including the diuretic hydrochlorothiazide, which is known to have decreased efficacy with increasing severity of kidney impairment. In the KDIGO \geq high risk group, edema events occurred at a higher frequency (55%) in patients who were switched from a more potent diuretic therapy (loop diuretics or >1 diuretic) to hydrochlorothiazide compared with those who did not decrease their diuretic therapy (31%). Adequate control of fluid homeostasis is important in the context of treatment with ERAs, particularly in patients with type 2 diabetes and those with a history of heart failure and kidney impairment. This can be achieved by diuretic therapy with thiazide and thiazide-like diuretics, such as hydrochlorothiazide and indapamide, or loop diuretics where required (eGFR <30 mL/min per 1.73 m²).^{16,50} Besides the continuation of loop diuretics, the European Society of Cardiology guidelines recommend indapamide, a thiazide-like diuretic, shown to be effective in patients with CKD stages 3 and 4.¹⁶ The SmPC specifies, in patients treated with loop diuretics before starting therapy with [aprocitentan], that the loop diuretic should not be switched to a less effective diuretic at initiation.²⁷ Together, these findings and recommendations highlight

the need for ensuring appropriate and optimal diuretic therapy for each patient before initiating aprocitentan in real-world clinical practice. Based on our clinical experience and data from the PRECISION trial, including data of participants with kidney impairment presented in this study, we also recommend ensuring a euvolemic state before initiation of aprocitentan. Finally, we suggest close monitoring of patients initiating aprocitentan, including consideration of the need for enhanced diuretic therapy if this is warranted.

Of the 7 participants with KDIGO \geq high risk who were hospitalized for heart failure events during PRECISION, all had a medical history of diabetes and either a medical history of heart failure or features, suggesting undiagnosed heart failure. All heart failure events resolved following treatment with loop diuretics, and none of these participants discontinued the study. The incidence of heart failure in this population is higher than in the overall phase 3 population²⁵: participants with KDIGO \geq high risk represent $\approx 20\%$ of the overall PRECISION population and contribute to the majority of hospitalizations due to heart failure (7 of 11 cases). However, study design features (such as decreased diuretic treatment when switching to SBAT before randomization) are obvious contributing factors.

As expected with ERAs, aprocitentan decreased hemoglobin concentrations ($\approx 8\%$) and increased estimated plasma volume ($\approx 14\%$) in participants with KDIGO \geq high risk. Both effects were reversible upon aprocitentan withdrawal (part 3).^{18,19} Interestingly, effects with aprocitentan 12.5 and 25 mg were similar, suggesting that the plasma volume expansion plateaued between these 2 doses, similar to the edema incidence. Reporting of anemia occurred more frequently in participants with KDIGO \geq high risk compared with the overall phase 3 population, in particular during part 1 of the study. This is not unexpected, as subjects with reduced kidney function typically have a lower baseline level of hemoglobin.^{51,52} Therefore, a mild decrease in the concentration of hemoglobin may trigger the reporting of an anemia event. Other measures, including NT-proBNP, potassium, sodium, and bodyweight, were only slightly or not affected. Baseline NT-proBNP was within expected levels for patients with CKD.^{53–55} A maximum change from baseline of 20% in NT-proBNP at week 36, after 32 weeks of aprocitentan 25 mg, and NT-proBNP concentrations remaining stable in both groups during part 3, is a reassuring safety observation. While measurement of NT-proBNP is currently not considered standard care in this patient population, thorough clinical assessment of volume status is recommended. Findings with parameters including bodyweight, hemoglobin, and NT-proBNP were compatible with the changes seen in plasma volume estimated by the Strauss formula. Formula-based estimates of plasma volume have been proven to provide prognostic value for clinical outcomes^{31,56–58}; however,

caution is advised in the interpretation of these estimates as a recent report in patients with clinically stable chronic heart failure demonstrated only limited reliability compared with quantitative volume measurements.⁵⁹

Aprocitentan does not aggravate the risk of hyperkalemia,^{26,27} and there is no need for monitoring potassium levels apart from common clinical practice. In contrast, the use of other antihypertensives, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, or MRA, can increase the risk of hyperkalemia, especially in patients with CKD.¹ Indeed, a major concern with MRAs in advanced CKD is the risk of hyperkalemia and further reduction in eGFR. For example, spironolactone is not recommended in patients with an eGFR <45 mL/min per 1.73 m² because of its increased risks of hyperkalemia and kidney function decline.^{10,15} While MRAs may often still be beneficial in these patients, close clinic and laboratory monitoring is required. Aprocitentan has no major impact on electrolytes and does not adversely affect eGFR aside from potential hemodynamic effects mediated by its BP-lowering capacity. Aprocitentan may represent the preferred choice in patients with uncontrolled hypertension and advanced CKD to improve BP control and reduce proteinuria if present.

CKD and RHT are both linked to an increased production of ET-1 and activation of the ET system. Aprocitentan as a dual ERA (ET_A/ET_B) was specifically selected for clinical development in difficult-to-treat hypertension.²⁰ It is conceivable that treatment with aprocitentan may elicit different effects compared with ET_A-selective ERAs.^{60–62} There is indirect evidence from clinical studies that compared with dual ERAs, ET_A-selective ERAs may be associated with a higher risk of fluid retention and heart failure, and increases in NT-proBNP.^{23,52,63–65} However, we are not aware of any published head-to-head studies assessing dual ERAs versus ET_A-selective ERAs in either hypertension and CKD,⁶⁶ and data from ET_A-selective ERAs cannot be extrapolated to dual ERAs or vice versa. In addition to receptor selectivity, the specific chemical and pharmacological properties of a drug need to be considered for the interpretation of differences in clinical outcomes.

Limitations of this analysis include its post hoc nature and the small sample size of the treatment arms in the KDIGO ≥high-risk group. Patients with NT-proBNP ≥500 pg/mL were excluded from the PRECISION study as per study protocol.²⁸ Long-term data (beyond the 48 weeks of PRECISION) are needed to conclusively assess the net benefit-risk of aprocitentan in patients with CKD and RHT; this is of particular importance for the assessment of effects on eGFR trajectories and CKD progression. As per the nature of this post hoc study, the analyses were not powered for evaluating statistical significance and should be interpreted descriptively. Strengths of the study include the 3-part study design of PRECISION,

allowing assessment of aprocitentan's efficacy (part 1) and the sustainability of its efficacy (parts 2 and 3). The similar results across the different subgroups with kidney impairment underpin aprocitentan's efficacy in lowering BP and UACR, suggesting a pronounced cardiovascular and kidney-protective effect.

PERSPECTIVES

Hypertension is difficult to treat in patients with CKD and is associated with an increased risk of morbidity and mortality compared with patients without CKD. Aprocitentan, a dual ET_A/ET_B receptor antagonist, is indicated in combination with other antihypertensives for the treatment of hypertension in adults not adequately controlled on other drugs. This is reflected in the recently published American College of Cardiology/American Heart Association guidelines.

In patients with kidney impairment and RHT, aprocitentan was generally well tolerated and efficiently lowered BP, particularly nighttime ambulatory BP, and markedly reduced UACR without reducing eGFR. Therefore, aprocitentan may confer a considerable, clinically meaningful cardiovascular and kidney-protective benefit in these difficult-to-treat patients. Aprocitentan may represent the preferred choice in patients with uncontrolled hypertension and advanced CKD to improve BP control and reduce proteinuria if present. Ultimately, long-term data from real-world clinical practice will assess the net benefit-risk of aprocitentan in these patients and provide insights on optimizing fluid management strategies.

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Supplemental Material

Tables S1–S12

Figures S1–S9

References (for Supplemental Tables and Figures)

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