#AHA22

SUSTAINED BLOOD PRESSURE LOWERING EFFECT WITH THE DUAL ENDOTHELIN RECEPTOR ANTAGONIST APROCITENTAN IN RESISTANT HYPERTENSION: RESULTS FROM A RANDOMIZED, CONTROLLED STUDY INCLUDING A WITHDRAWAL PHASE

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on behalf of the PRECISION investigators.

American Heart Association.

Disclosures

Markus Schlaich has received institutional grants or contracts from Medtronic, Abbott, and ReCor; personal consulting fees from Medtronic, Abbott, and ReCor; personal payment or honoraria from Medtronic, Abbott, Merck, and Servier; personal support for attending meetings and/or travel from Medtronic and Abbott; and serves as the President of HBPRCA and on the ISH Scientific Committee.

Michael Weber has received consulting fees/performed research services for Janssen, Bristol Myers Squibb, CinCor, Medtronic, ReCor, and Ablative Solutions.

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Ji-Guang Wang has no competing interests to declare.

Parisa Danaietash and Roland Dreier are employees of Idorsia Pharmaceutical Ltd and hold stock or stock options in Idorsia Pharmaceutical Ltd.

Marc Bellet and Mouna Sassi-Sayadi are employees of Idorsia Pharmaceutical Ltd.

Lloyd Haskell is an employee of Janssen and holds stock in Janssen, LLC.

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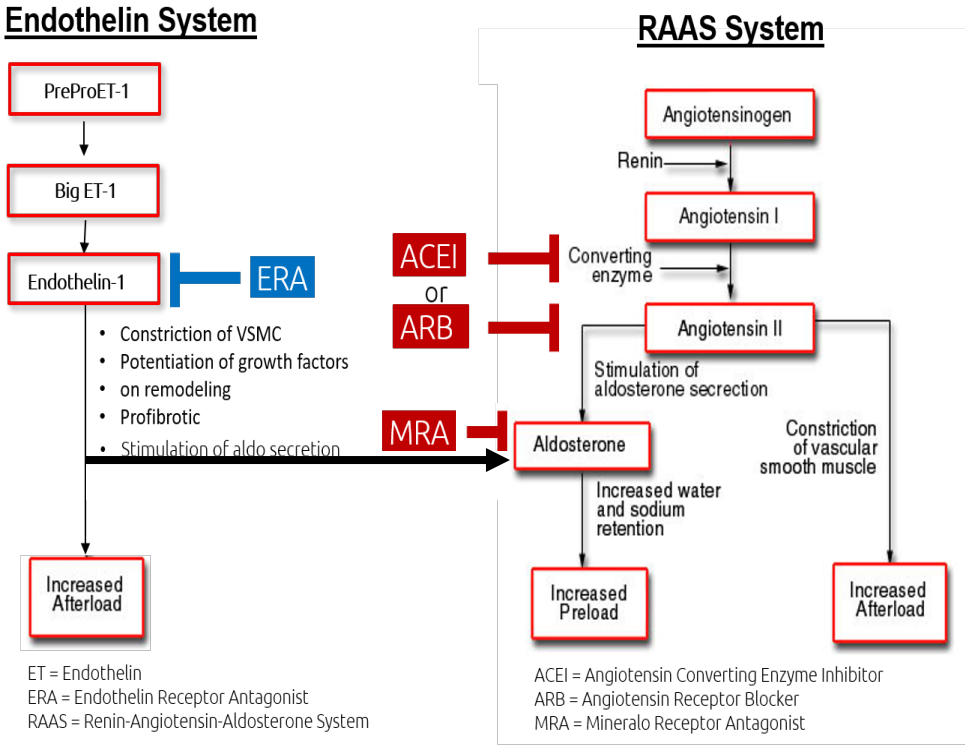
Background

- Failure to control BP with currently available drugs suggests that relevant physiologic pathways remain unopposed
- RHT patients are at increased cardiovascular risk[1] and are poly-medicated; any new therapy proposed as fourth-line must offer a positive benefit-risk ratio on top of existing background therapies and frequent concomitant treatments of comorbidities
- Endothelin (ET) has been implicated in the pathogenesis of hypertension[2,3]
- Aprocitentan is a dual ET_A/ET_B receptor antagonist (ERA) investigated in the phase 3 PRECISION study



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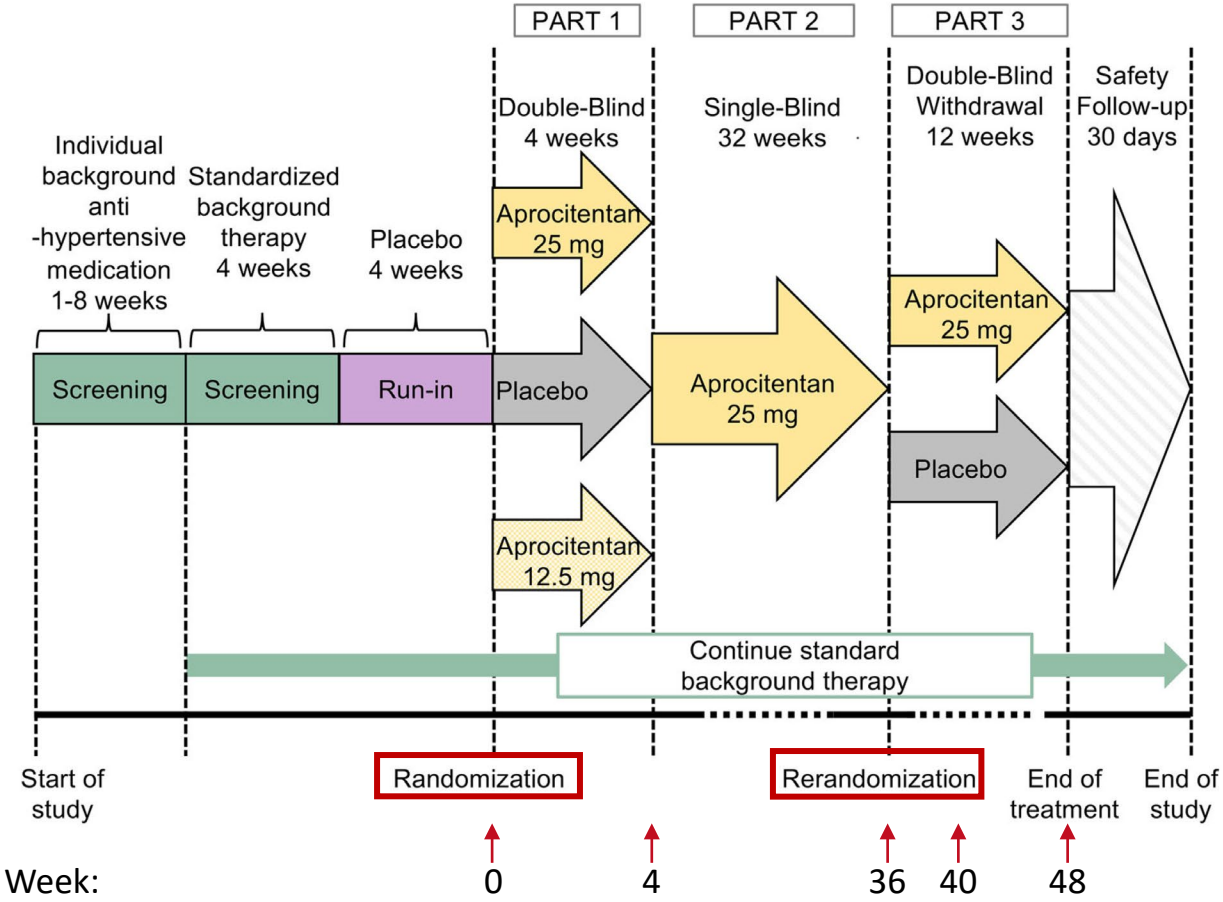
3. Clozel M. *Can J Physiol Pharmacol*. 2022;100(7):573-583. doi: 10.1139/cjpp-2022-0010.

Study Design and Methods



Primary endpoint:

- Change from baseline to Week 4 (PART 1) in mean trough sitting office SBP

Key secondary endpoint:

- Change from withdrawal baseline (Week 36) to Week 40 (PART 3) in mean trough sitting office SBP

Other secondary endpoint:

- Changes in 24-h ambulatory BP at Week 4 and Week 40

Danaietash P, et al. *J Clin Hypertens*. 2022;24(7):804-813. doi: 10.1111/jch.14517.

Study Population

Key inclusion criteria:[1]

- History of uncontrolled office BP despite ≥3 antihypertensive medications
- Unattended sitting office SBP ≥140 mmHg

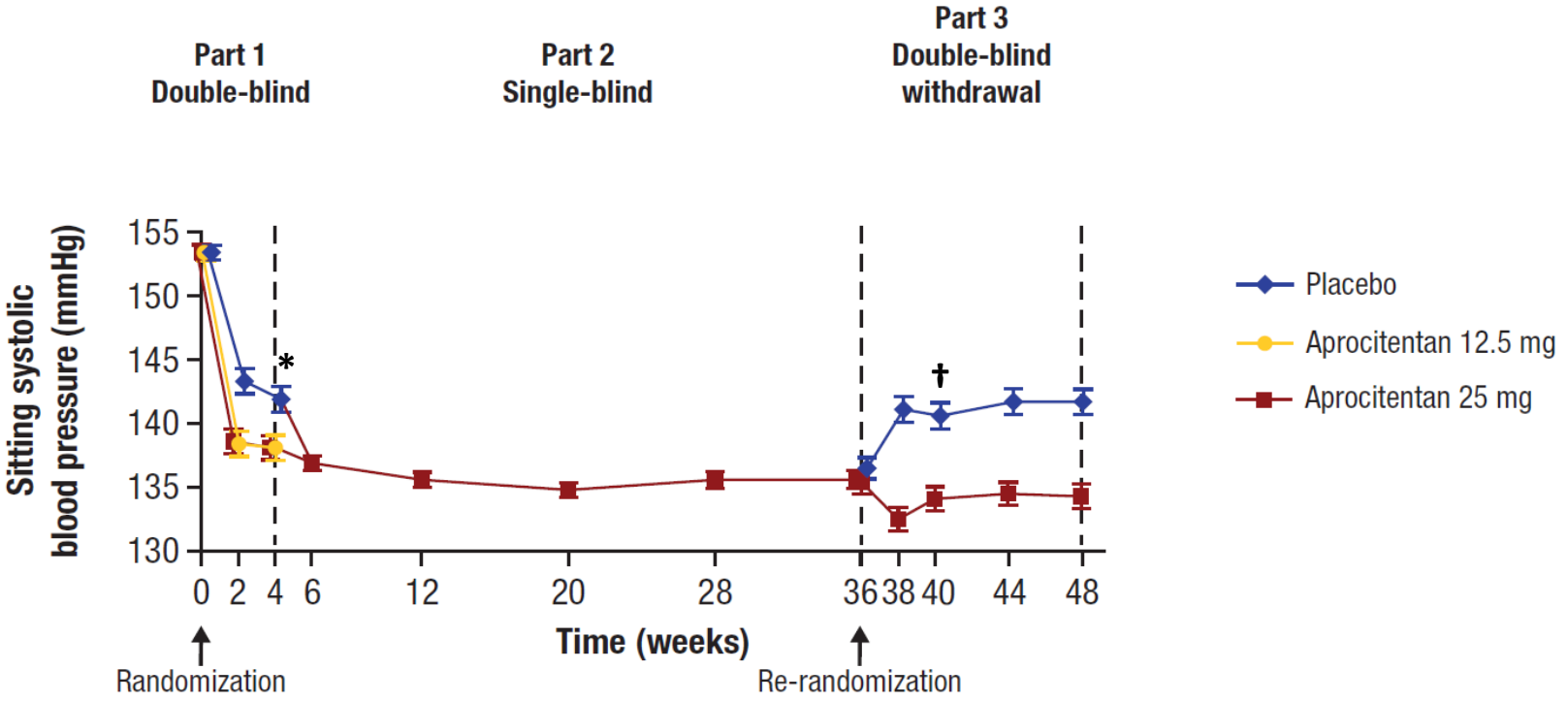
Key exclusion criteria:[1]

- Confirmed severe hypertension (grade 3)
- Major cardiovascular, renal, cerebrovascular medical complications in the past 6 months or NYHA stage III-IV heart failure
- N-terminal pro-BNP levels ≥500 pg/ml
- eGFR <15 ml/min/1.73 m^2

Characteristic	Aprocitentan 12.5 mg (n=243)	Aprocitentan 25 mg (n=243)	Placebo (n=244)
Age (years) at screening	61.2	61.7	62.2
Men	59%	60%	59%
Race			
White	84%	82%	83%
Black/African American	12%	12%	11%
Asian	5%	6%	5%
BMI (kg/m^2) at screening	33.6	34.3	33.3
eGFR at baseline between 15 and <60 mL/min/1.73 m^2	23%	25%	19%
UACR (mg/g) at baseline	(n=241)	(n=238)	(n=238)
<30	60%	65%	65%
30-300	26%	23%	24%
>300	14%	12%	12%
≥4 BP drugs at screening	62%	65%	62%
uAOBP at baseline (mmHg)	153/88	153/88	153/87
ABPM at baseline (mmHg)	138/84	138/83	137/83
History of heart failure	20%	21%	18%
History of diabetes mellitus	54%	56%	52%

1. Danaietash P, et al. *J Clin Hypertens*. 2022;24(7):804-813. doi: 10.1111/jch.14517.

Unattended Office Systolic Blood Pressure

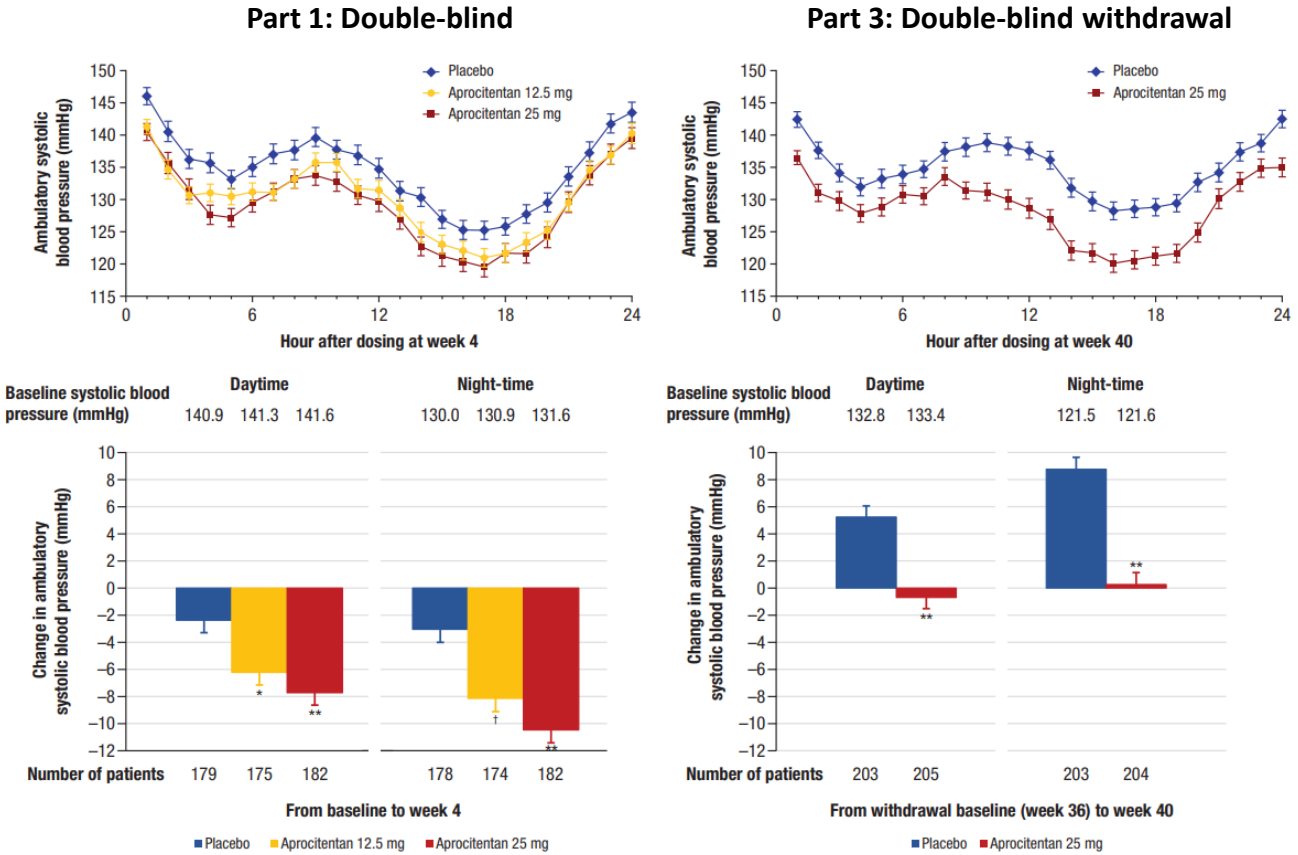


*Primary endpoint.
P=0.0042 for aprocitentan 12.5 mg vs placebo.
P=0.0046 for aprocitentan 25 mg vs placebo.

†Key secondary endpoint.
P<0.0001 for aprocitentan 25 mg vs placebo.

Bars are standard error of the mean. Values are offset from each other for readability.

24-Hour Ambulatory Systolic Blood Pressure



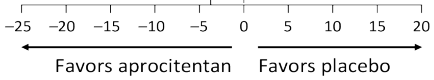
Bars are standard error of the mean.

*P=0.003, †P=0.0002, **P<0.0001 (for comparison with placebo). No correction for multiplicity was applied.

Subgroup Analysis/Change in UACR

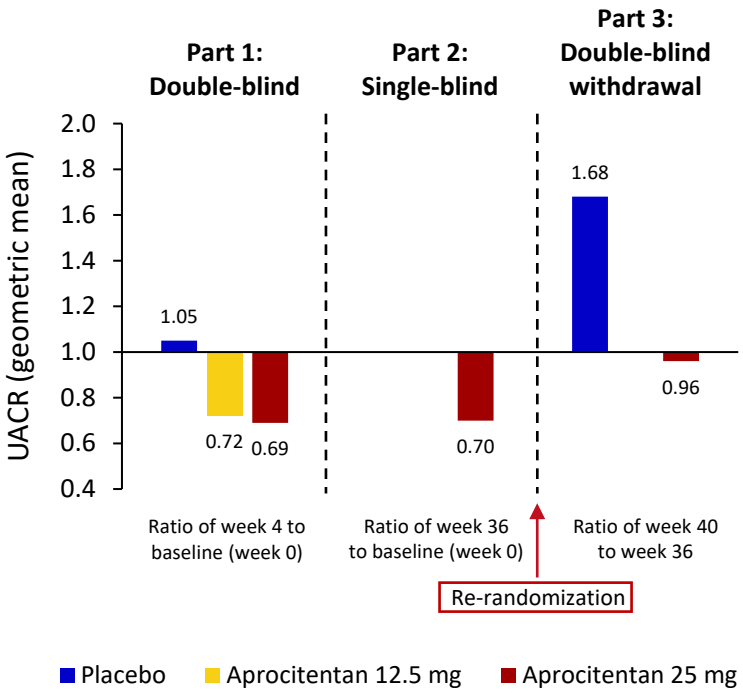
Subgroup Analysis

Treatment subgroup	Aprocitentan	Placebo	LS mean (95% CI)	Interaction p-value
Overall				
	223	224	−3.79 (−6.38, −1.20)	
	231	224	−3.73 (−6.30, −1.15)	
Age				0.1559
18-<65 years	130	121	−2.18 (−5.63, 1.27)	
	130	121	−1.70 (−5.15, 1.76)	
65-<75 years	73	78	−5.64 (−10.2, −1.11)	
	81	78	−4.63 (−9.02, −0.24)	
≥75 years	20	25	−6.75 (−15.3, 1.76)	
	20	25	−12.85 (−21.4, −4.26)	
UACR at baseline				0.1009
<30.0 mg/g	131	144	−3.27 (−6.48, −0.07)	
	149	144	−2.19 (−5.30, 0.91)	
30-300 mg/g	60	50	−3.34 (−8.45, 1.77)	
	52	50	−5.33 (−10.7, −0.02)	
>300 mg/g	30	24	−11.72 (−19.3, −4.18)	
	28	24	−11.84 (−19.5, −4.17)	
eGFR at baseline				0.0008
eGFR ≥60 ml/min/1.73 m²	174	185	−3.14 (−5.98, −0.30)	
	174	185	−1.26 (−4.11, 1.59)	
eGFR 15-<60 ml/min/1.73 m²	49	39	−7.45 (−13.5, −1.40)	
	57	39	−13.33 (−19.2, −7.45)	



- Aprocitentan 12.5 mg vs placebo
- Aprocitentan 25 mg vs placebo

Change in UACR over time
Overall population



Treatment-emergent Adverse Events of Special Interest

Study part	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Placebo
PART 1 Double-blind (4 weeks)	**(n=243)**	**(n=245)**	**(n=242)**
Patients with at least one event, n (%)	31 (12.8)	47 (19.2)	7 (2.9)
Edema/fluid retention	22 (9.1)	45 (18.4)	5 (2.1)
Severe AE*	0	3	0
Additional diuretic used	10	21	3
Discontinued study treatment	0	1	0
Hospitalization for heart failure	0	2 (0.8)	0
Part 2 Single-blind (32 weeks)		**(n=704)**	
Patients with at least one event, n (%)		188 (26.7)	
Edema/fluid retention		128 (18.2)	
Severe AE*		3	
Additional diuretic used		63	
Discontinued study treatment		5	
Hospitalization for heart failure		6 (0.9)	
Part 3 Double-blind withdrawal (12 weeks)		**(n=310)**	**(n=303)**
Patients with at least one event, n (%)		20 (6.5)	16 (5.3)
Edema/fluid retention		8 (2.6)	4 (1.3)
Severe AE*		1	0
Additional diuretic used		3	3
Discontinued study treatment		1	0
Hospitalization for heart failure		2 (0.6)	1 (0.3)

*Event that may cause noticeable discomfort and usually interferes with daily activities. The patient may not be able to continue in the study, and treatment or intervention is usually needed.

Conclusions

- Aprocitentan lowered both standardized automated office and 24-hour ambulatory BP compared to placebo after 4 weeks
- The BP lowering effect was maintained over 48 weeks
- Edema/fluid retention was the most common AE reported with aprocitentan within the first 4 weeks of treatment
    - Events were clinically manageable with the addition/up-titration of diuretic therapy
- Dual ET antagonism with aprocitentan may represent a new alternative pharmacological approach to treat resistant hypertension

THANK YOU

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Scientific Sessions

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