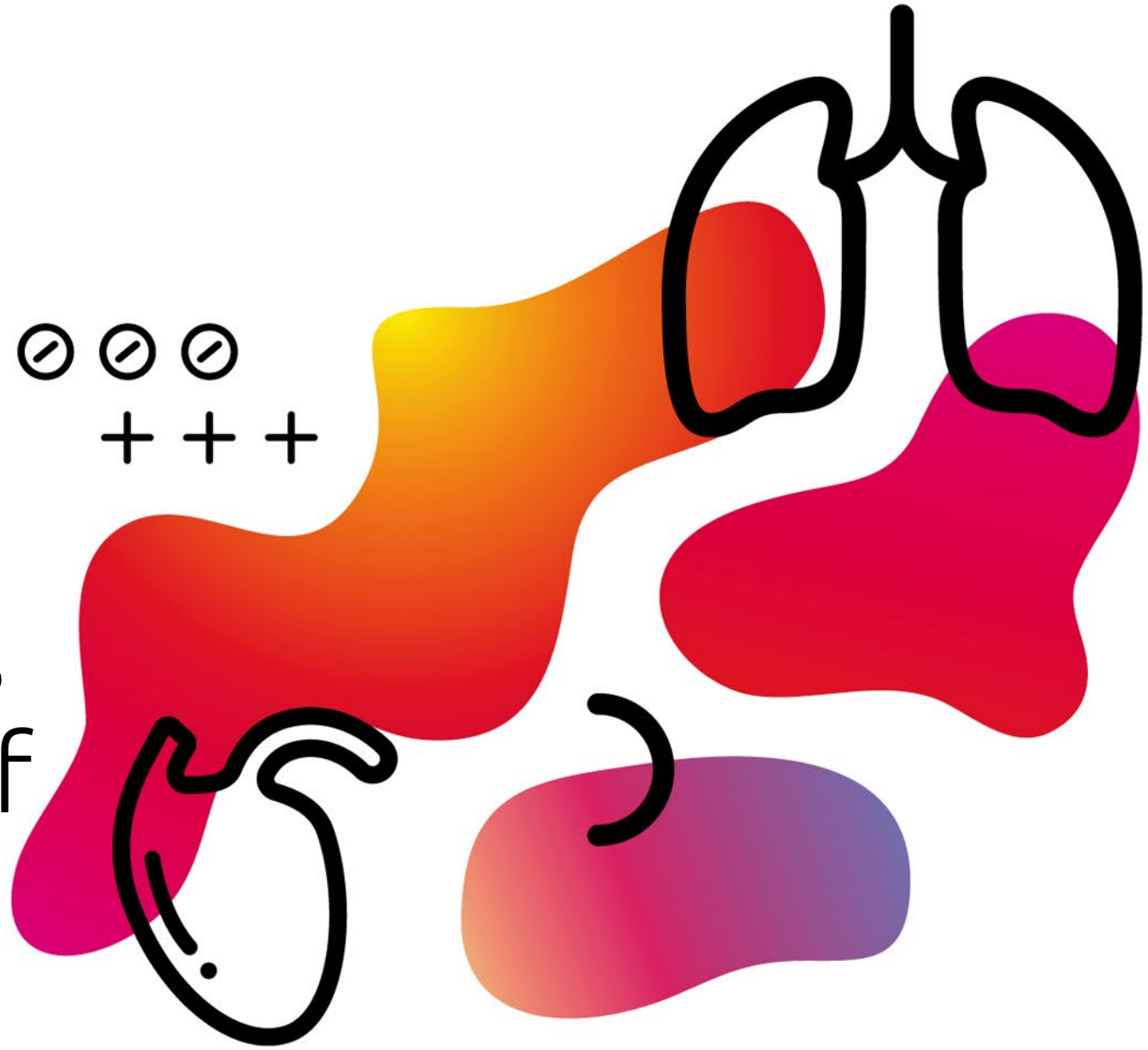
idorsia

The Lancet and AHA late-breaking science session reports the results of Phase 3 study of aprocitentan



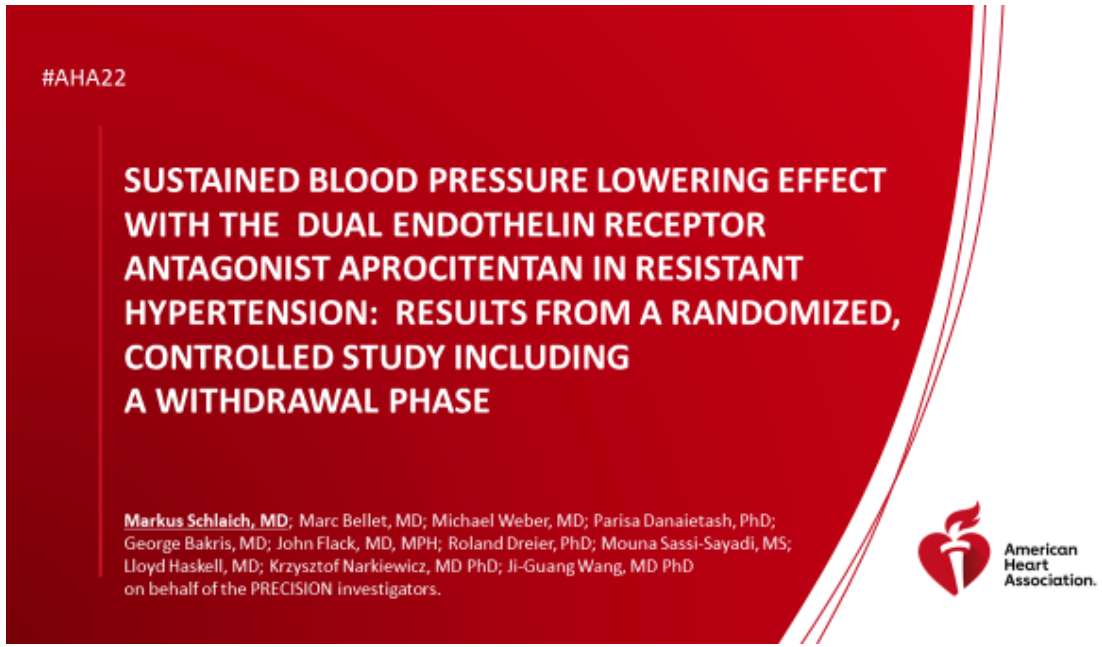
Investor webcast – November 2022

The following information contains certain “forward-looking statements”, relating to the company’s business, which can be identified by the use of forward-looking terminology such as “estimates”, “believes”, “expects”, “may”, “are expected to”, “will”, “will continue”, “should”, “would be”, “seeks”, “pending” or “anticipates” or similar expressions, or by discussions of strategy, plans or intentions. Such statements include descriptions of the company’s investment and research and development programs and anticipated expenditures in connection therewith, descriptions of new products expected to be introduced by the company and anticipated customer demand for such products and products in the company’s existing portfolio. Such statements reflect the current views of the company with respect to future events and are subject to certain risks, uncertainties and assumptions. Many factors could cause the actual results, performance or achievements of the company to be materially different from any future results, performances or achievements that may be expressed or implied by such forward-looking statements. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected.

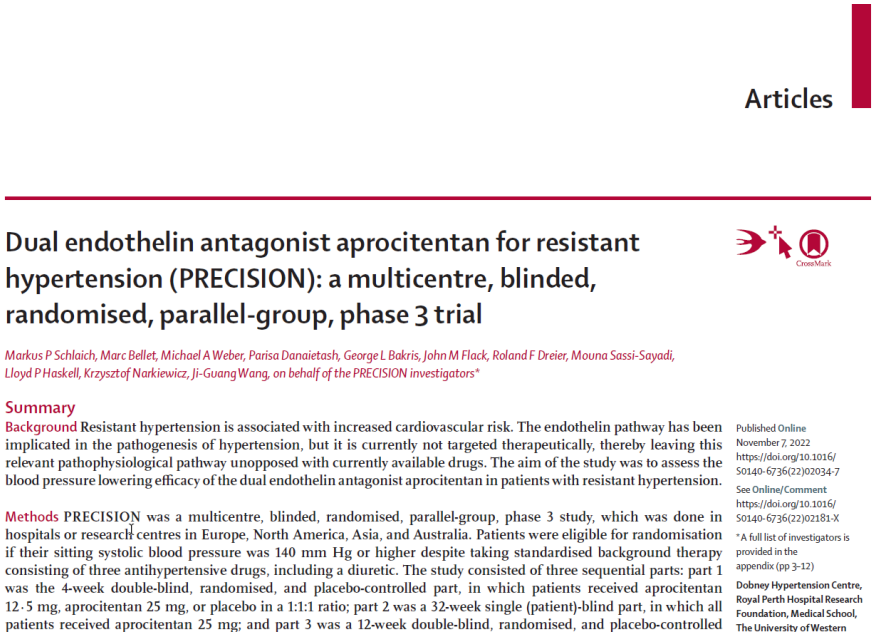
"I'm delighted that we are able to share the data from PRECISION, released simultaneously yesterday, both in a late-breaking presentation at the AHA meeting and in the primary manuscript."

Martine Clozel
Chief Scientific Officer

Simultaneous Publication



American Heart Association (AHA) Scientific Sessions 2022



Schlaich MP, et al. Lancet. Published online November 7, 2022

30 years of researching the endothelin system

1988

Endothelin-1 identified

1990

ET_A and ET_B receptors identified

1993

First orally available ERA published in *Nature*

1998

First evidence of dual ERA effect in hypertension published in *New England Journal of Medicine*

2007

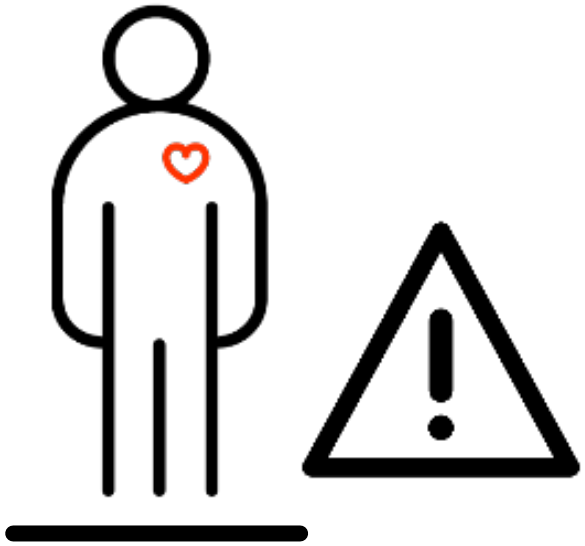
Failed attempt in resistant hypertension with selective ERA

2022

Aprocitentan – positive Phase 3 results for resistant hypertension

Aprocitentan is investigational, in development and not approved or marketed in any country.

What is resistant hypertension?



Resistant hypertension

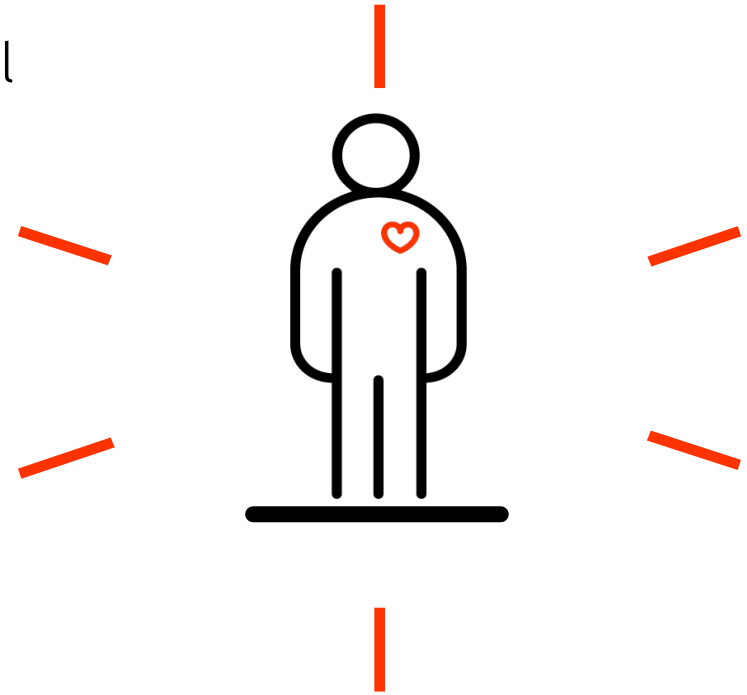
Patients whose blood pressure remains high, despite receiving at least three antihypertensives of different pharmacological classes, including a diuretic, at optimal dose.

Risk factors for resistant hypertension

Older age; especially
> 75 years

Post-menopausal
women

Ethnicity
(higher prevalence in
African Americans)



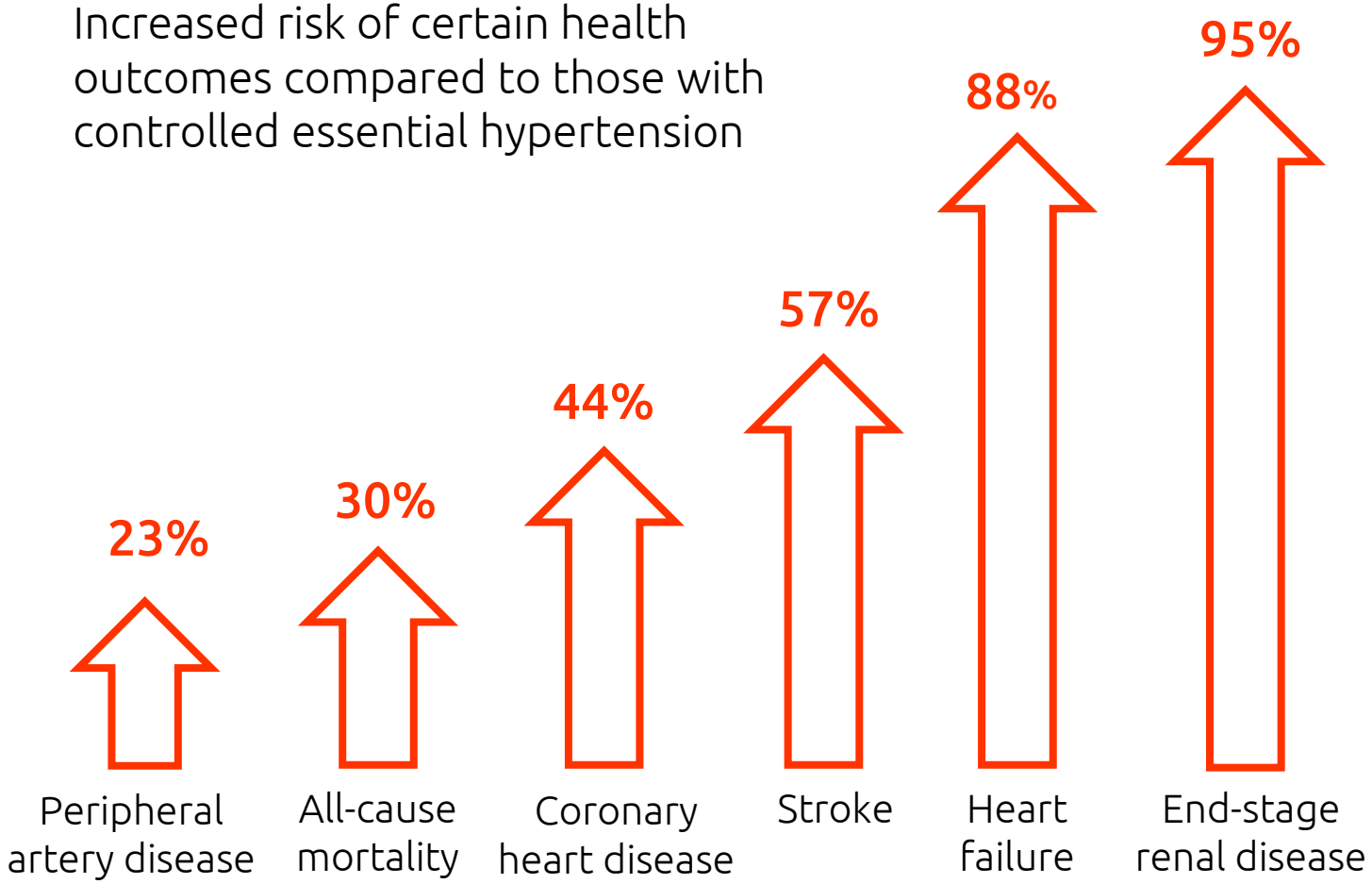
High Body Mass
Index (BMI)

Obstructive Sleep
Apnea (OSA)

High baseline blood
pressure and chronicity of
uncontrolled hypertension

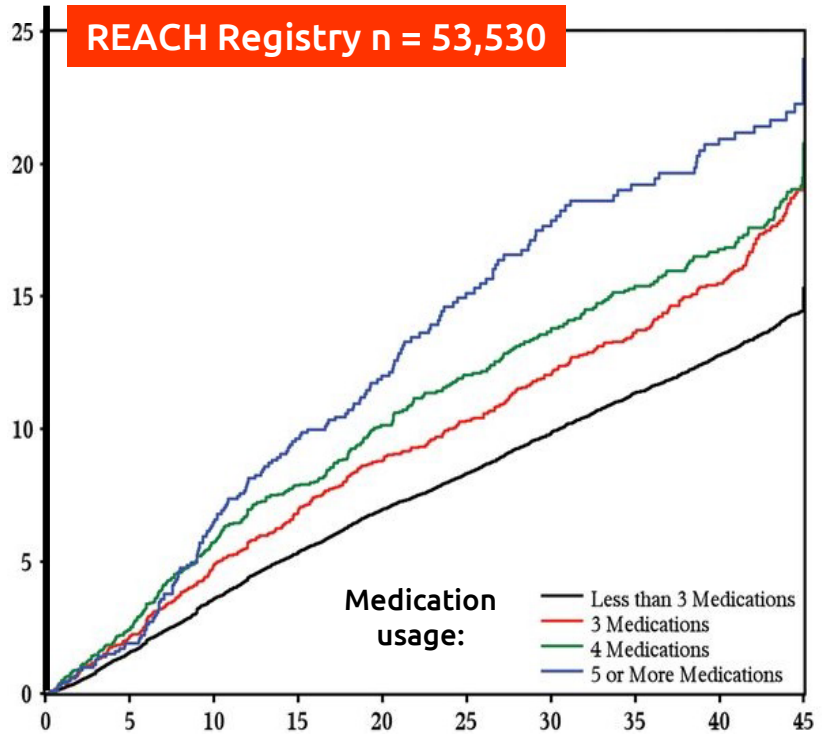
Disease burden when hypertension is uncontrolled

Increased risk of certain health outcomes compared to those with controlled essential hypertension



Muntner et al., 2014

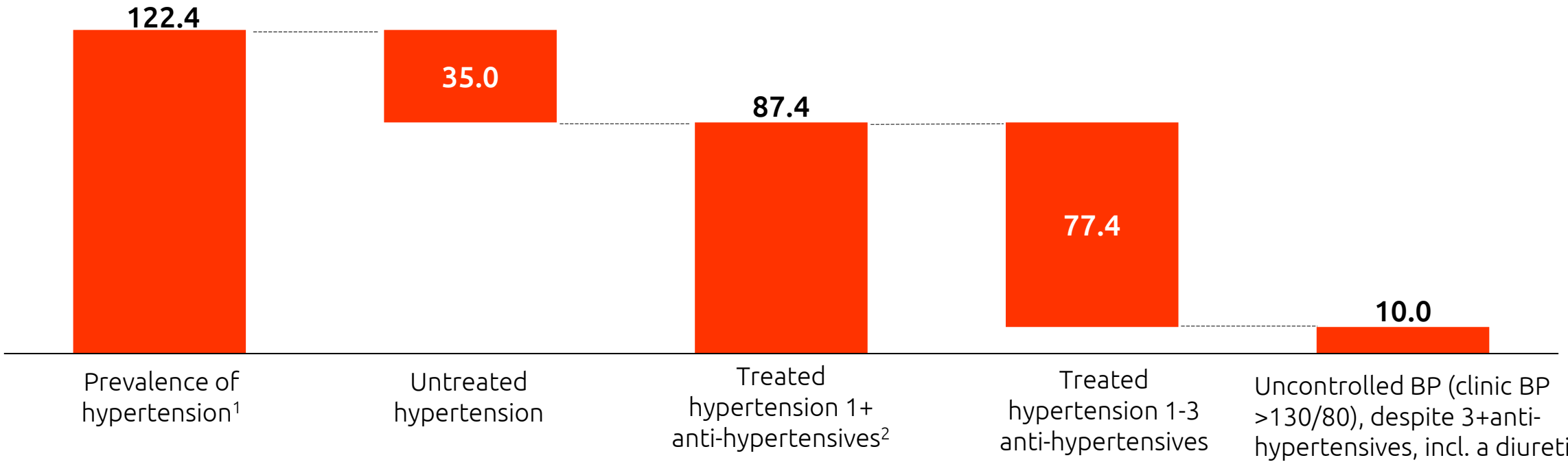
Higher incidence of major cardiovascular events



European Heart Journal, 2013

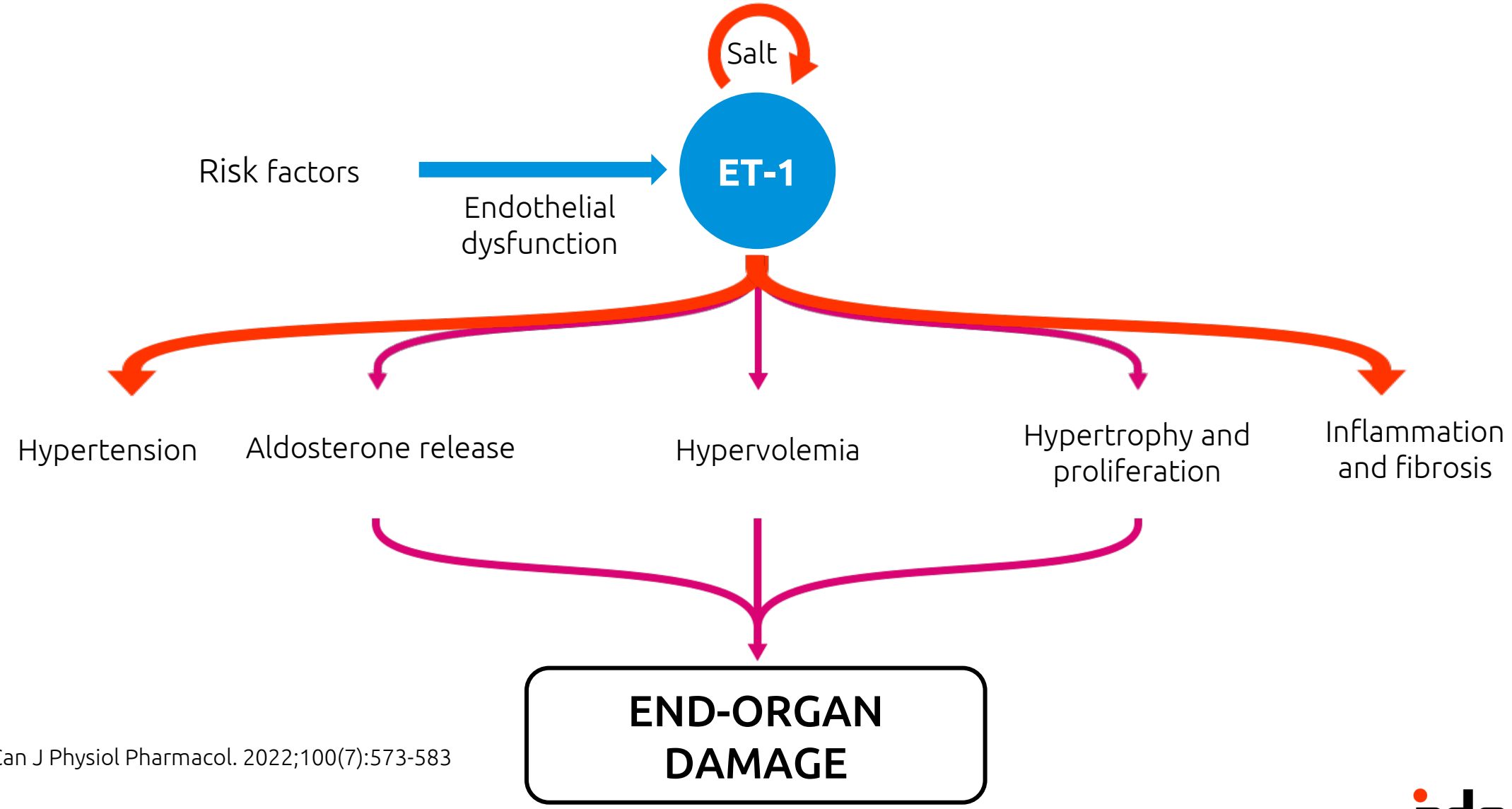
Estimated resistant hypertensive patient population in 2025

US breakdown of projected number of resistant hypertensive patients (patients in millions, 2025)



(1) Estimated 269.6 mn US adults in 2025 (US census) and HTN prevalence measure in 2017-2018 (45.4%) with BP threshold levels 130/80 mmHg, from NHANES 2017-2018
(2) HTN population receiving pharmacological treatment 2017-2018, NHANES data from 2017-2018 report and age-adjusted treatment rate of 71.4%. (*Hypertension.* 2022; 79:207–217)
(3) Applying a RHT prevalence rate of 11.4% among patients treated with a thiazide diuretic, using the 2018 AHA/ACC BP threshold for RHT (Clinic BP >130/80) (Hypertension. 2019; 73(2):424-431)

Endothelin system in resistant hypertension

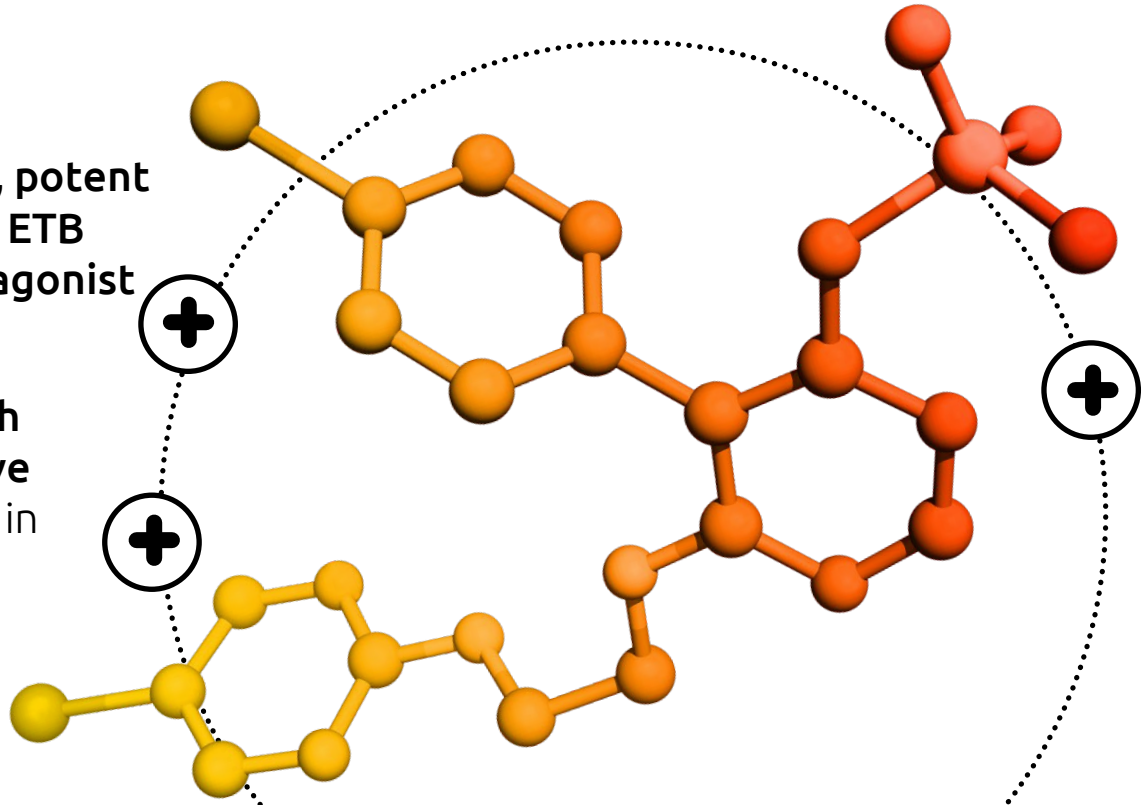


Clozel M. Can J Physiol Pharmacol. 2022;100(7):573-583

Aprocitentan in resistant hypertension

Orally-active, potent dual ETA and ETB receptor antagonist

Synergistic effect with other antihypertensive drugs (RAAS blockers) in animal models



Low potential for drug-drug interaction

Demonstrated efficacy of aprocitentan on blood pressure, renal and cardiac protection in animal models of salt-dependent hypertension

Demonstrated blood pressure decrease in patients with essential hypertension

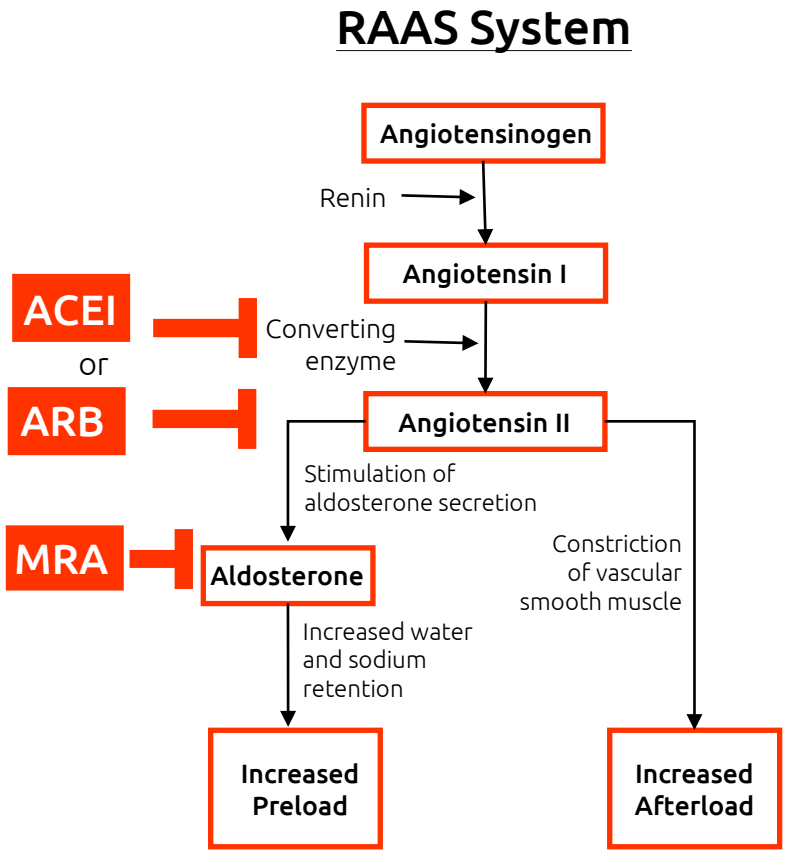
Aprocitentan is investigational, in development and not approved or marketed in any country.

"The Phase 3 PRECISION study establishes aprocitentan as a promising new therapeutic approach to achieve sustained blood pressure lowering with a manageable safety profile, in patients with resistant hypertension."

Prof. Markus Schlaich, MD, FAHA, FESC, ISHF
The University of Western Australia / Royal Perth Hospital and an investigator in the PRECISION study

Aprocitentan is investigational, in development and not approved or marketed in any country.

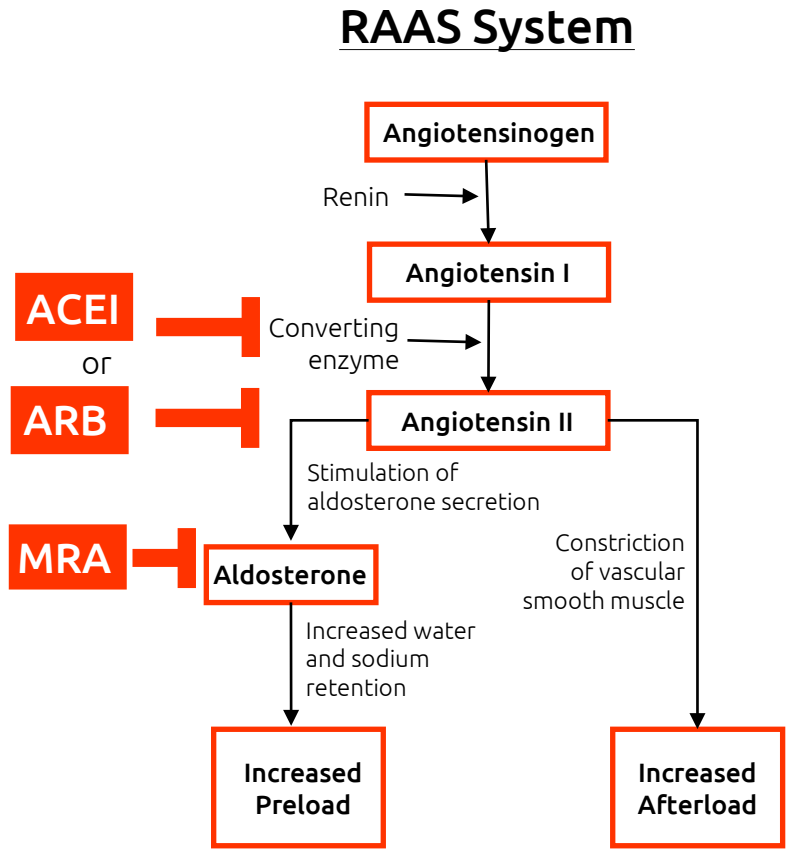
Background



RAAS = Renin-Angiotensin-Aldosterone System
ACEI = Angiotensin Converting Enzyme Inhibitor
ARB = Angiotensin Receptor Blocker
MRA = Mineralo Receptor Antagonist

Background

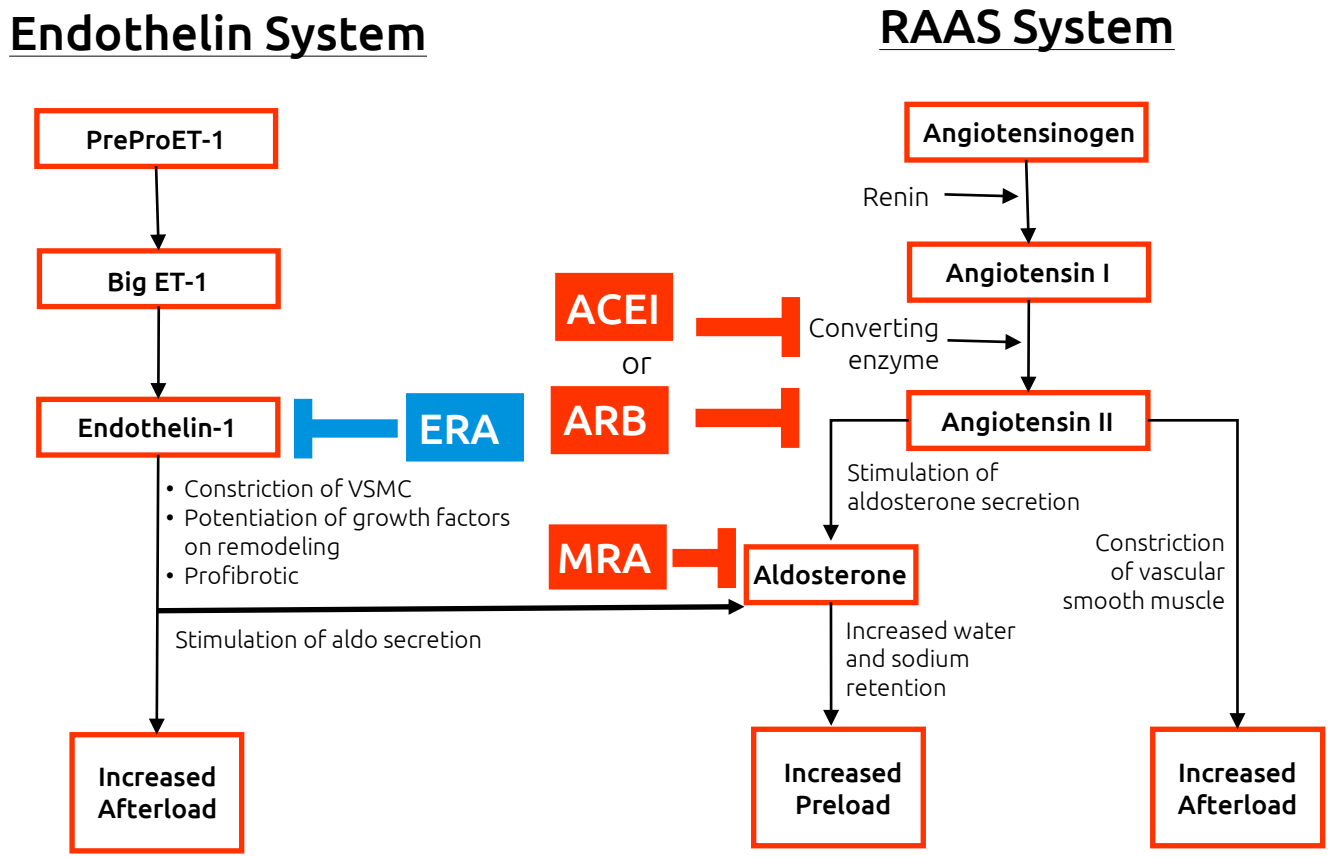
- Failure to control blood pressure (BP) with currently available drugs suggests that relevant physiologic pathways remain unopposed



RAAS = Renin-Angiotensin-Aldosterone System
ACEI = Angiotensin Converting Enzyme Inhibitor
ARB = Angiotensin Receptor Blocker
MRA = Mineralo Receptor Antagonist

Background

- Failure to control blood pressure (BP) with currently available drugs suggests that relevant physiologic pathways remain unopposed
- Endothelin (ET) has been implicated in the pathogenesis of hypertension[1,2]



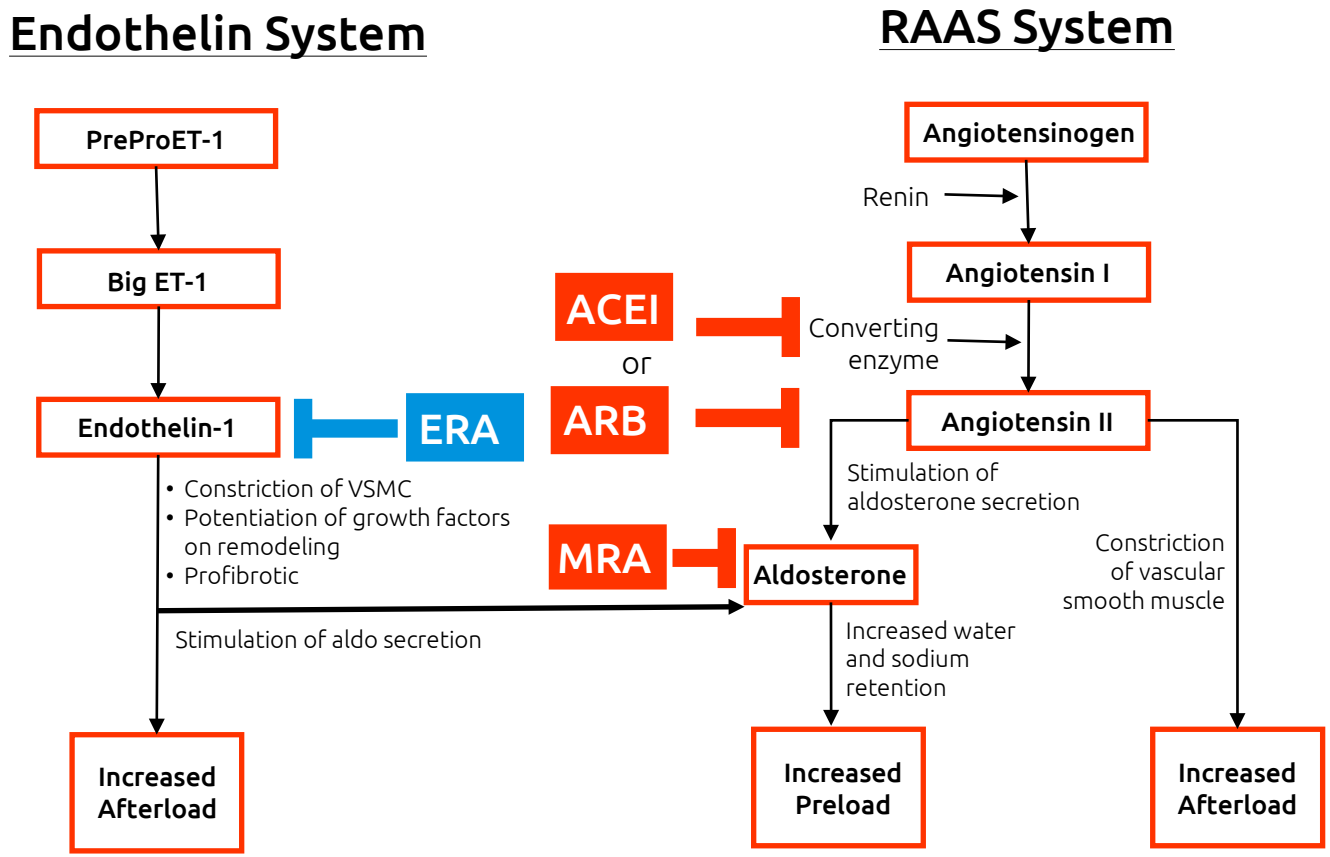
ET = Endothelin
ERA = Endothelin Receptor Antagonist

RAAS = Renin-Angiotensin-Aldosterone System
ACEI = Angiotensin Converting Enzyme Inhibitor
ARB = Angiotensin Receptor Blocker
MRA = Mineralo Receptor Antagonist

1. Dhaun N, et al. Hypertension. 2008;52(3):452-459
2. Clozel M. Can J Physiol Pharmacol. 2022;100(7):573-583

Background

- Failure to control blood pressure (BP) with currently available drugs suggests that relevant physiologic pathways remain unopposed
- Endothelin (ET) has been implicated in the pathogenesis of hypertension[1,2]
- Aprocitentan is a dual ET_A/ET_B receptor antagonist (ERA) investigated in the Phase 3 PRECISION study



ET = Endothelin
ERA = Endothelin Receptor Antagonist

RAAS = Renin-Angiotensin-Aldosterone System
ACEI = Angiotensin Converting Enzyme Inhibitor
ARB = Angiotensin Receptor Blocker
MRA = Mineralo Receptor Antagonist

1. Dhaun N, et al. Hypertension. 2008;52(3):452-459
2. Clozel M. Can J Physiol Pharmacol. 2022;100(7):573-583

Aprocitentan is investigational, in development and not approved or marketed in any country.

PRECISION Phase 3 study

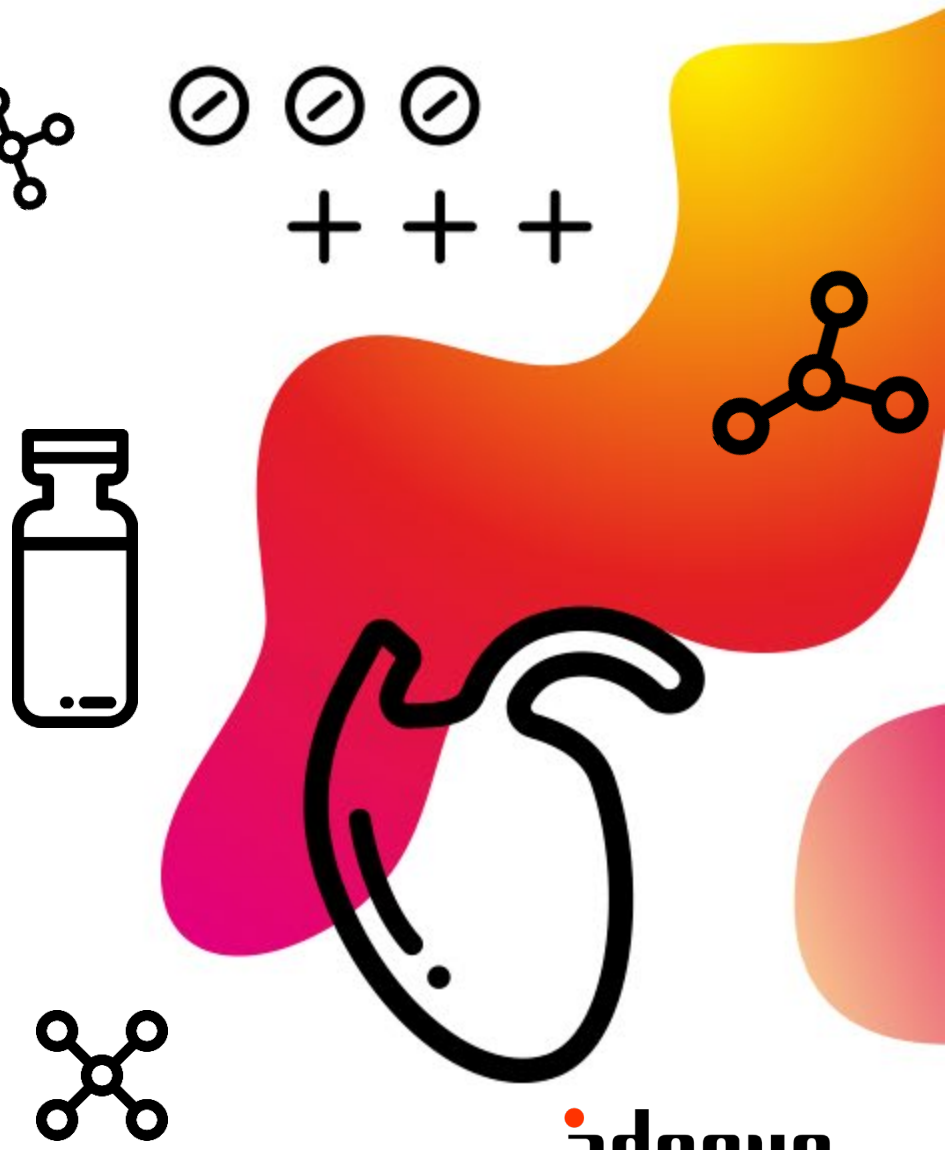
Primary objective

Demonstrate the blood pressure lowering effect of aprocitentan in patients with confirmed resistant hypertension

Secondary objectives

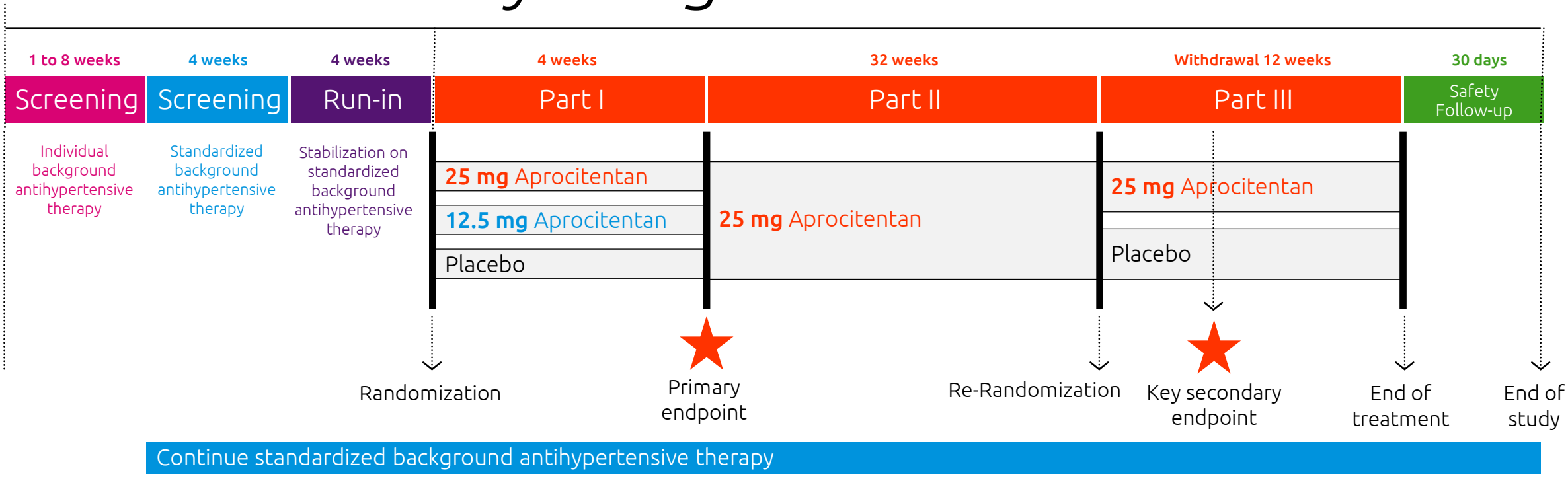
Demonstrate that the effect of aprocitentan on blood pressure is durable in patients with confirmed resistant hypertension

To evaluate the long-term safety and tolerability of aprocitentan in patients with confirmed resistant hypertension during 48 weeks of treatment



Aprocitentan is investigational, in development and not approved or marketed in any country.

PRECISION study design & methods



Primary endpoint

Change from baseline to Week 4 (Part 1) in mean trough sitting office systolic BP (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-hour ambulatory BP at Week 4 and Week 40

Danaietash P, et al. J Clin Hypertens. 2022;24(7):804-813

Aprocitentan is investigational, in development and not approved or marketed in any country.

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]

- Major cardiovascular, renal, cerebrovascular medical complications in the past 6 months or New York Heart Association stage III-IV heart failure
- N-terminal pro-BNP levels ≥500 pg/ml
- Estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2

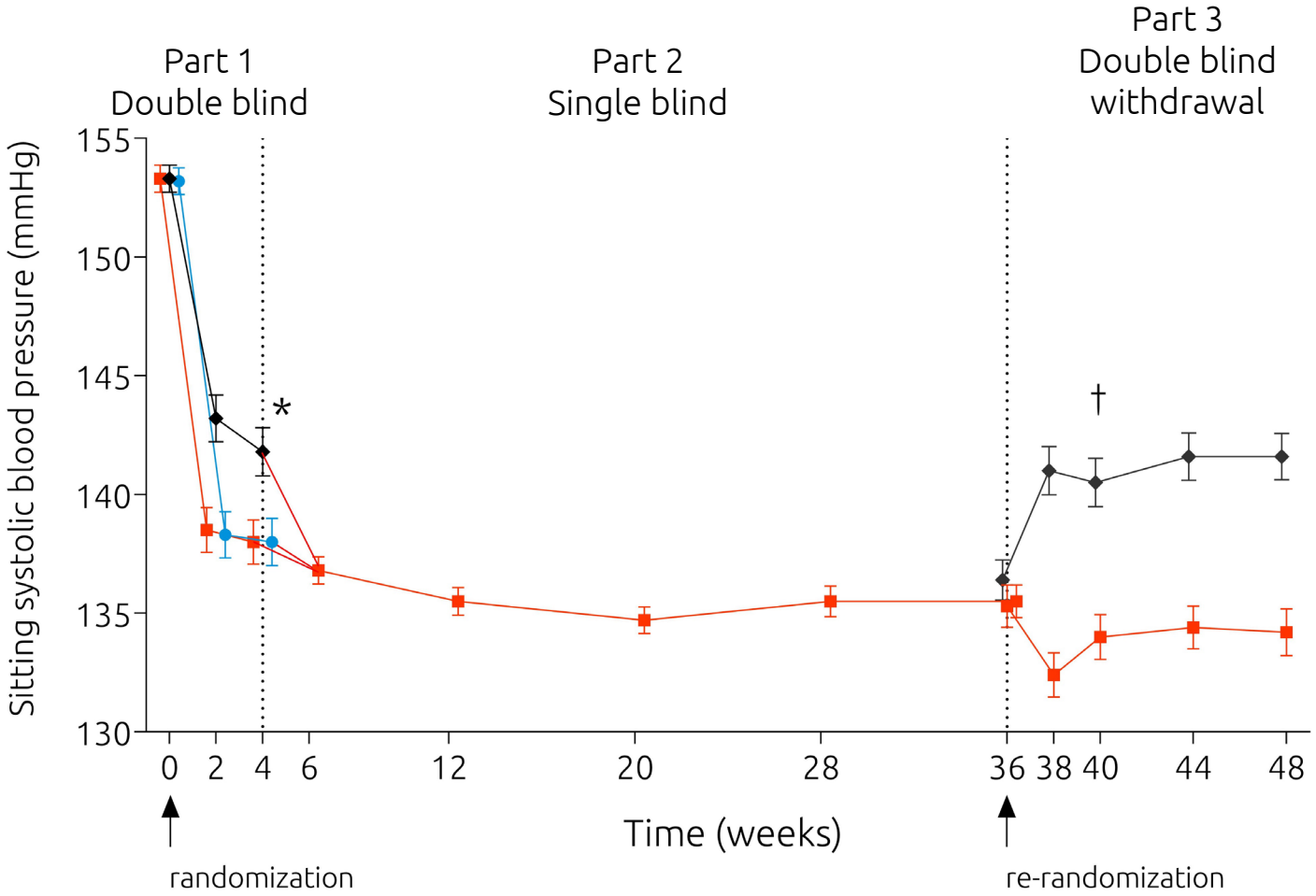
Characteristic	Aprocitentan 12.5 mg (n=243)	Aprocitentan 25 mg (n=243)	Placebo (n=244)
Age (years) at screening	61.2	61.7	62.2
uAOBP at baseline (mmHg)	153/88	153/88	153/87
ABPM at baseline (mmHg)	138/84	138/83	137/83
Men	59%	60%	59%
Race			
White	84%	82%	83%
Black/African American	12%	12%	11%
Asian	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%
History of heart failure	20%	21%	18%
History of diabetes mellitus	54%	56%	52%

BMI = Body mass index; UACR = Urine Albumin-Creatinine Ratio;
uAOBP = unattended automated office BP; ABPM = Ambulatory BP monitoring

1. Danaietash P, et al. J Clin Hypertens. 2022;24(7):804-813

Aprocitentan is investigational, in development and not approved or marketed in any country.

Aprocitentan has significant and sustained efficacy



Placebo

Aprocitentan 12.5 mg

Aprocitentan 25 mg

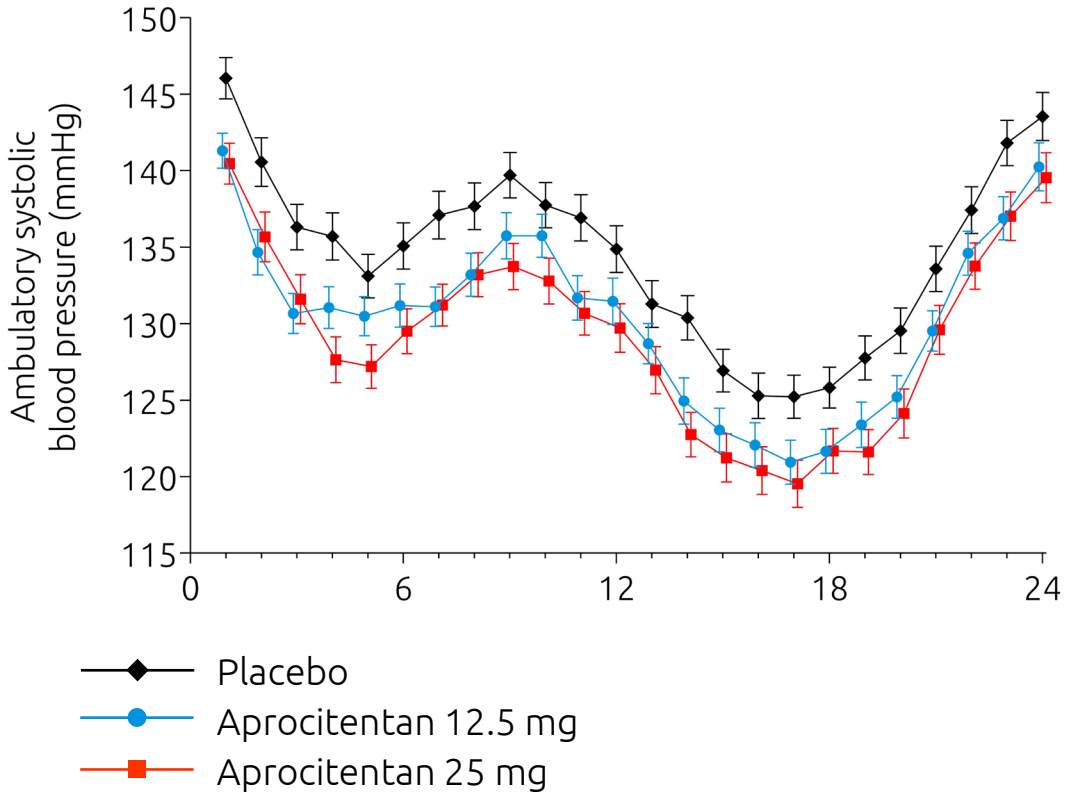
***Primary endpoint**
P=0.0042 for aprocitentan 12.5 mg vs placebo
P=0.0046 for aprocitentan 25 mg vs placebo

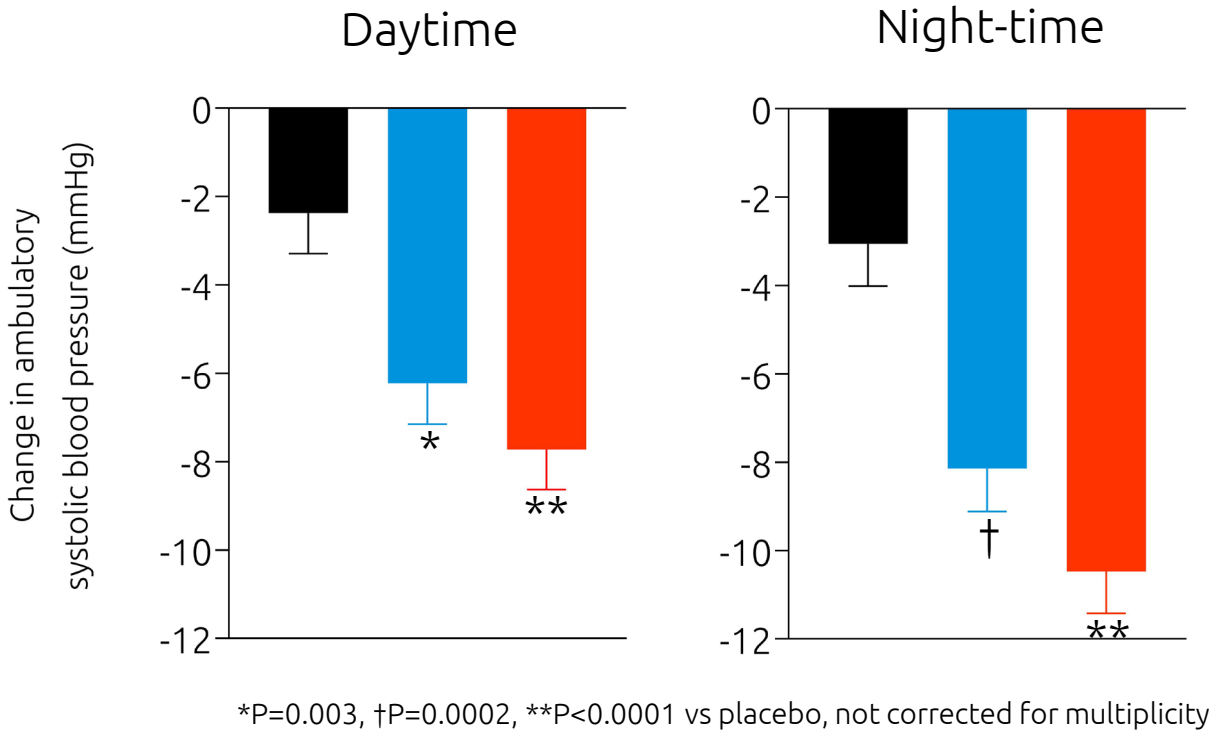
†Key secondary endpoint
P<0.0001 for aprocitentan 25 mg vs placebo

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

Aprocitentan is investigational, in development and not approved or marketed in any country.

Efficacy confirmed by Ambulatory BP monitoring at Week 4 (DB Part 1)



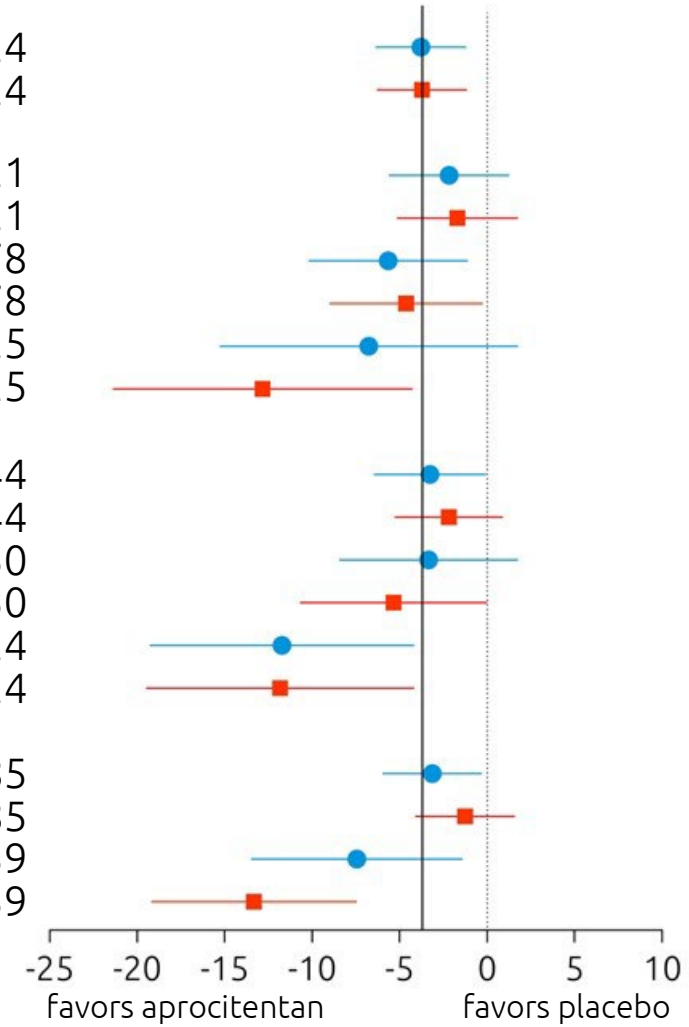


Bars are standard error of the mean
Values are offset from each other for readability

Aprocitentan is investigational, in development and not approved or marketed in any country.

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 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
≥60 ml/min/1.73m^2	174	185	-3.14	(-5.98, -0.30)	
	174	185	-1.26	(-4.11, 1.59)	
15 - <60 ml/min/1.73m^2	49	39	-7.45	(-13.5, -1.40)	
	57	39	-13.33	(-19.2, -7,45)	

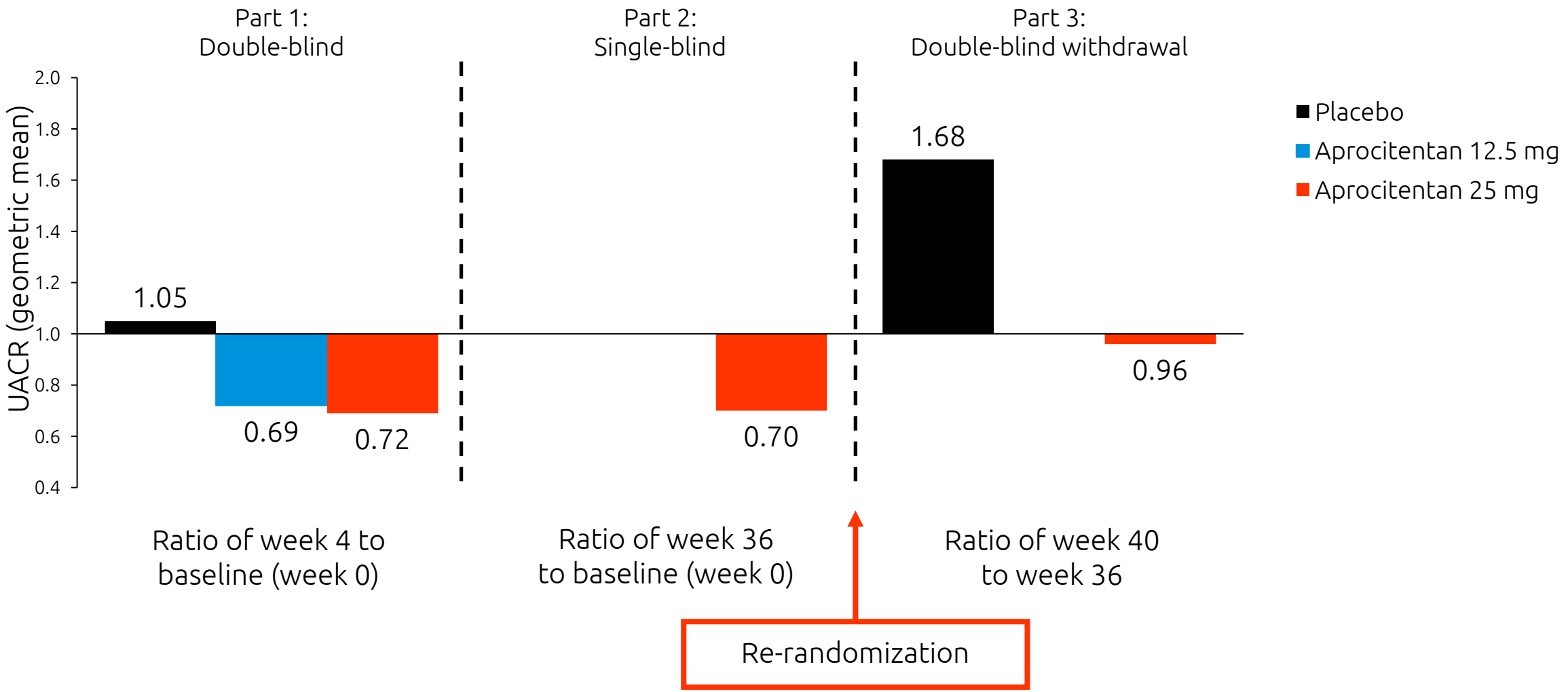


- Aprocitentan 12.5 mg vs placebo
- Aprocitentan 25 mg vs placebo

Aprocitentan is investigational, in development and not approved or marketed in any country.

Change in Urine Albumin-Creatinine Ratio over time

Overall population



Aprocitentan is investigational, in development and not approved or marketed in any country.

Adverse events summary

Study Part	Randomized treatment group	(n)	Adverse Events (AEs) %	AEs leading to discontinuation %	Serious AEs %
Double blind Part 1 4 Weeks	Aprocitentan 12.5 mg	243	27.6	2.9	3.3
	Aprocitentan 25 mg	245	36.7	2	3.3
	Placebo	242	19.4	0.8	1.2
Single blind Part 2 32 weeks	Aprocitentan 25 mg	704	61.2	3.8	11.6
Double blind withdrawal Part 3 12 weeks	Aprocitentan 25 mg	310	38.4	2.3	5.8
	Placebo	303	33.7	1.7	3

Selected Treatment-emergent Adverse Events of Special Interest

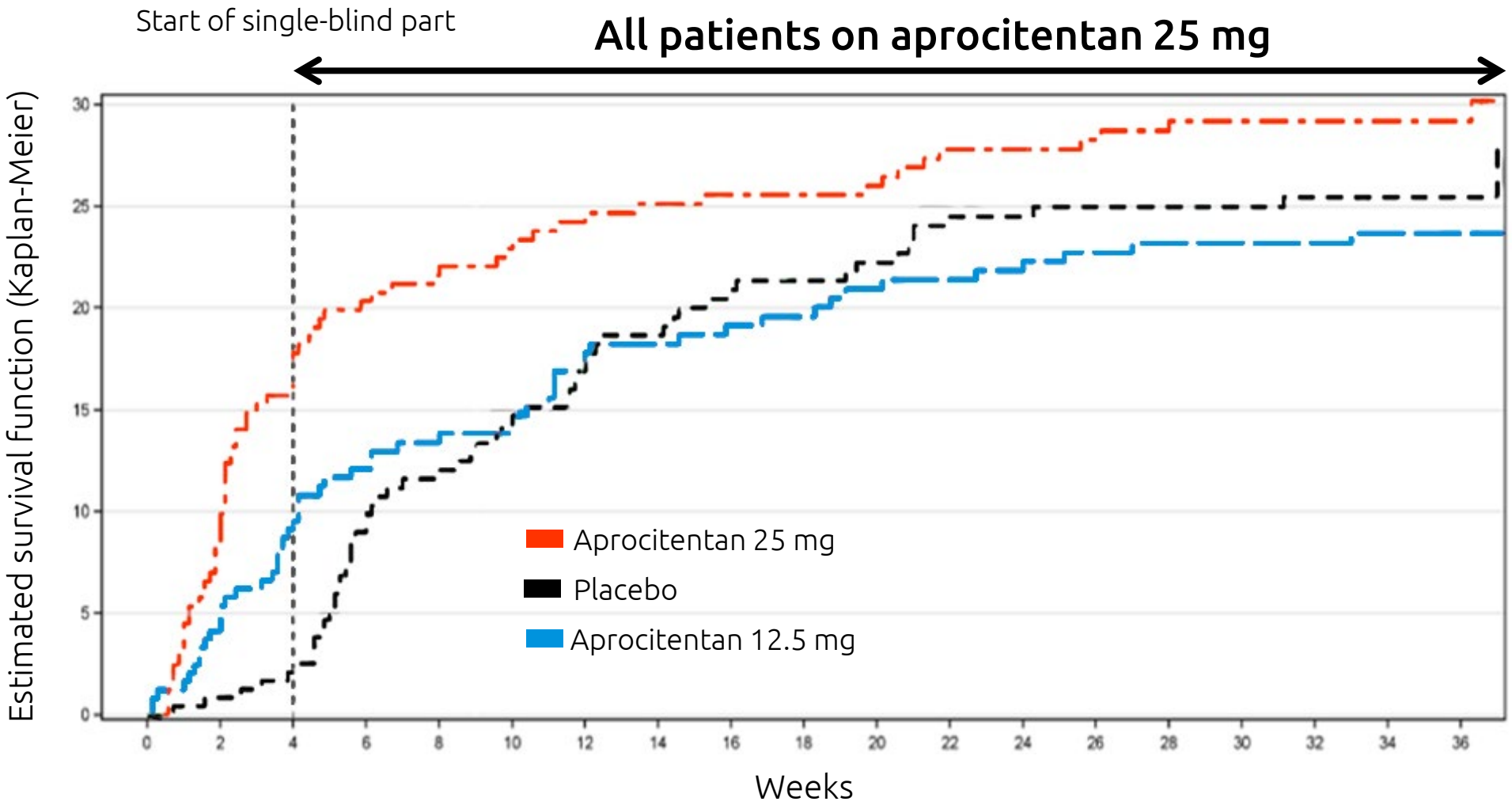
Study part	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Placebo
Part 1 Double-blind (4 weeks)	**(n=243)**	**(n=245)**	**(n=242)**
Edema/fluid retention	22 (9.1)	45 (18.4)	5 (2.1)
Severe AE*	0	3	0
Additional diuretic used	10	21	3
Discontinued study treatment	0	1	0
Part 2 Single-blind (32 weeks)		**(n=704)**	
Edema/fluid retention		128 (18.2)	
Severe AE*		3	
Additional diuretic used		63	
Discontinued study treatment		5	
Part 3 Double-blind withdrawal (12 weeks)		**(n=310)**	**(n=303)**
Edema/fluid retention		8 (2.6)	4 (1.3)
Severe AE*		1	0
Additional diuretic used		3	3
Discontinued study treatment		1	0

*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

Aprocitentan is investigational, in development and not approved or marketed in any country.

Majority of Adverse Events occurred within the first 4 weeks

Time to first AE of edema fluid retention



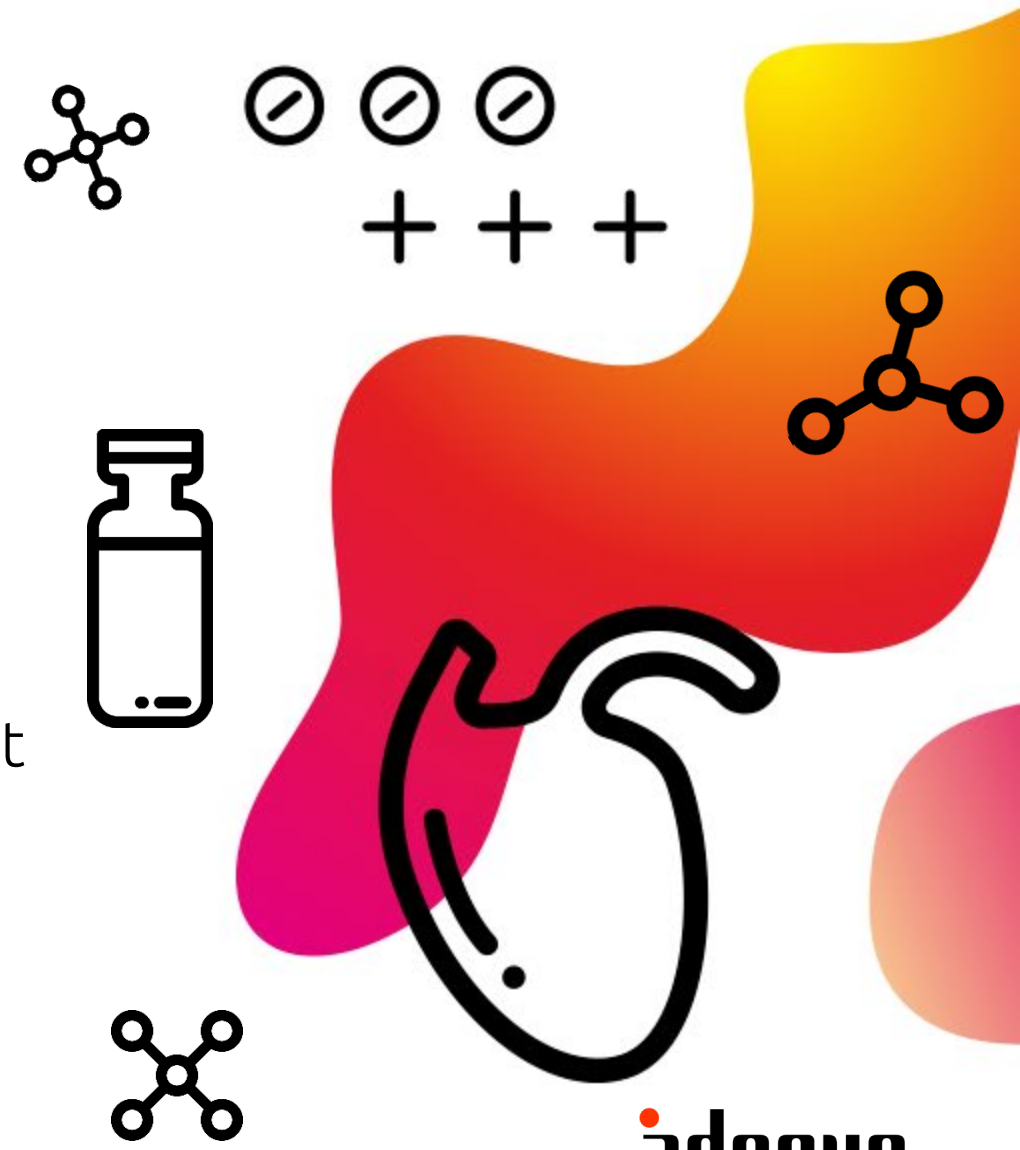
Adverse events of heart failure (48 Weeks)

History of heart failure: ~20% + multiple other risk factors

- **Non-serious Heart Failure (n = 8)**
  - No death
  - 1 case on aprocitentan 12.5 mg and 7 on aprocitentan 25 mg
  - No discontinuation
  - 7 out of 8 cases were judged unrelated to treatment by the investigator
  - 5 out of 8 patients were treated with diuretics
- **Hospitalizations for Heart Failure (n = 11)**
  - No death
  - 1 case on placebo and 10 on aprocitentan 25 mg
  - All patients were diabetic
  - 6 out of 11 patients with CKD 3-4
  - 5 out of 11 patients had a history of heart failure
  - 2 patients were discontinued
  - All patients were treated with diuretics
  - All 11 cases were judged unrelated to treatment by the investigator

Conclusion

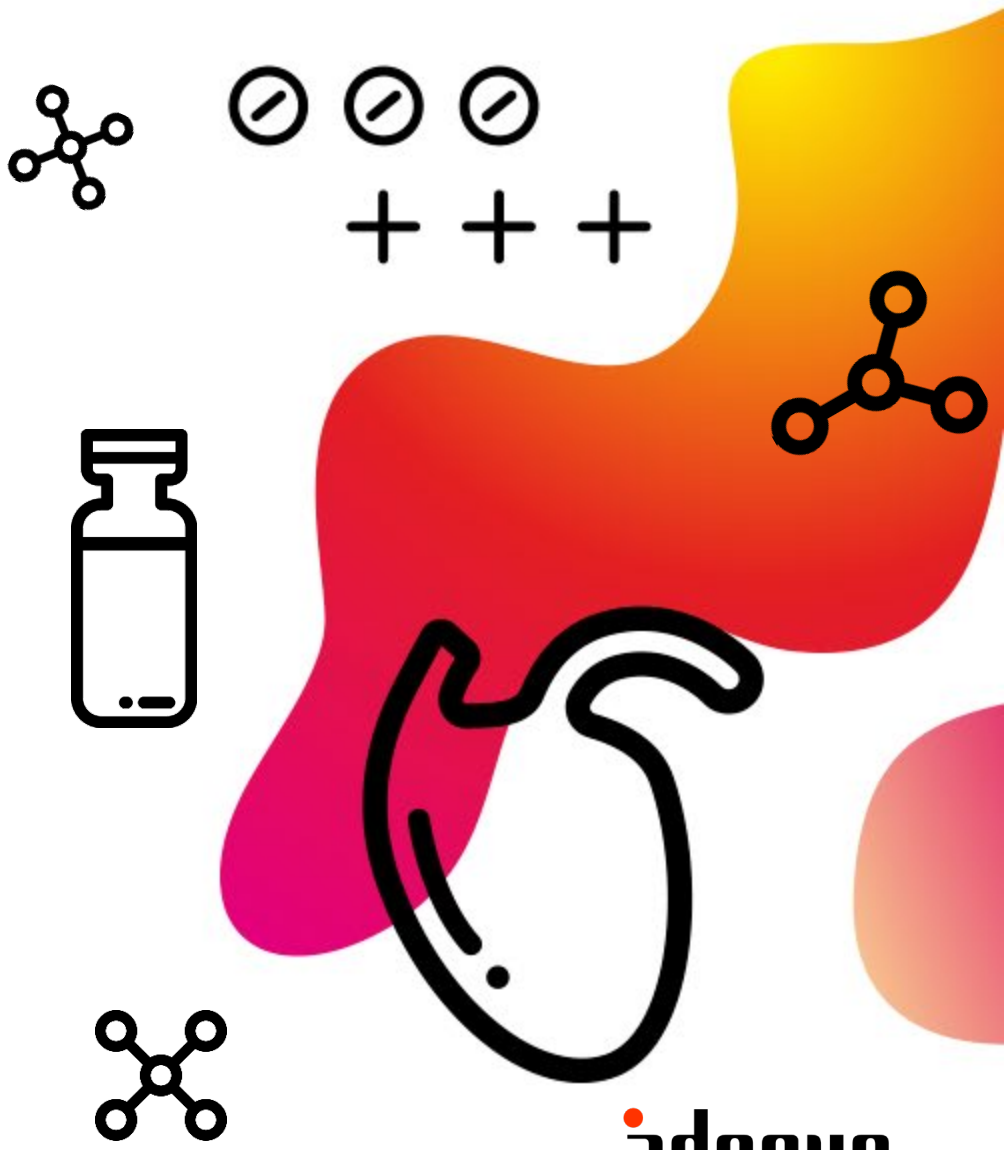
- PRECISION studied patients with true resistant hypertension at high cardiovascular risk and including CKD patients
- Aprocitentan lowered office and 24-hour ambulatory BP after 4 weeks and over 48 weeks
- Edema/fluid retention was reported with aprocitentan within the first weeks of treatment
  - Events were clinically manageable with the addition of diuretic therapy



Aprocitentan is investigational, in development and not approved or marketed in any country.

Conclusion

The dual ET_A/ET_B antagonist aprocitentan may represent a new approach to treat resistant hypertension



Aprocitentan is investigational, in development and not approved or marketed in any country.