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Aprocitentan and the endothelin system in resistant hypertension

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Abstract

Endothelin has emerged as a target for therapeutic intervention in systemic hypertension. As a vasoconstrictor, comitogenic agent, linking pulse pressure and vascular remodeling, and mediator of aldosterone and catecholamine release, endothelin is a key player in hypertension and end-organ damage. In 10%–20% of the hypertensive population, the high blood pressure is resistant to administration of antihypertensive drugs of different classes in combination. Because endothelin is not targeted by the current antihypertensive drugs, this may suggest that this resistance is due, in part at least, to a dependence on endothelin. This hypothesis is supported by the observation that this form of hypertension is often salt-sensitive, and that the endothelin system is stimulated by salt. In addition, the endothelin system is activated in subjects at risk of developing resistant hypertension, such as African Americans or patients with obesity or obstructive sleep apnea. Aprocitentan is an investigational, novel, potent, dual endothelin receptor antagonist (ERA) currently in phase 3 development for the treatment of difficult-to-treat hypertension. This article discusses the research that underpinned the discovery of this ERA and the choice of its first clinical indication for patients with forms of hypertension that cannot be well controlled with classical antihypertensive drugs.

Key words: aprocitentan, endothelin receptor antagonist, resistant hypertension, endothelin

Résumé

L'endothéline s'est révélée constituer une cible pour des interventions thérapeutiques en cas d'hypertension systémique. Comme agent vasoconstricteur et comitogène liant la tension pulsatile au remodelage vasculaire, ainsi que comme médiateur de la libération d'aldostérone et de catécholamines, l'endothéline joue un rôle clé dans l'hypertension et l'atteinte des organes cibles. Chez 10 à 20 % de la population atteinte d'hypertension, la tension artérielle élevée est résistante à l'administration de médicaments antihypertenseurs de diverses classes en association. Puisque l'endothéline n'est pas la cible des médicaments antihypertenseurs actuels, il est possible que cette résistance soit, au moins en partie, dépendante de l'endothéline. Cette hypothèse est fondée sur l'observation que cette forme d'hypertension est souvent sensible à l'apport sodé, et que l'endothéline est stimulée par le sel. De plus, le système endothéline est activé chez des sujets à risque élevé d'hypertension résistante, comme les Afro-Américains ou les patients atteints d'obésité ou d'apnée obstructive du sommeil. L'aprocitentan est un nouveau double antagoniste des récepteurs ET_A et ET_B de l'endothéline (ARE) puissant qui est en ce moment en phase 3 de développement pour le traitement de l'hypertension difficile à traiter. Cet article se penche sur la recherche qui a sous-tendu la découverte de cet ARE, de même que sur le choix de sa première indication clinique chez les patients présentant des formes d'hypertension que l'on ne peut pas maîtriser convenablement à l'aide de médicaments antihypertenseurs classiques. [Traduit par la Rédaction]

Mots-clés : aprocitentane, antagoniste des récepteurs de l'endothéline, hypertension résistante, endothéline

Introduction

The exciting discovery of endothelin-1 (ET-1) as the most potent vasoconstrictor peptide (Yanagisawa et al. 1988) sparked profound research efforts to understand the ET system and its key physiological and pathophysiological roles. While its major role in regulating blood pressure was quickly established (Clozel et al. 1993; Cardillo et al. 1999), it was also soon recognized that it was not merely a vasoconstrictor, but rather a multifunctional peptide that acts in a paracrine and autocrine manner to regulate vascular tone, cell proliferation, fibrosis, inflammation, and secretion of cytokines, catecholamines, and aldosterone, thus affecting many fundamental cellular processes in health and disease (Kedzierski and Yanagisawa 2001).

In our quest to understand the pathogenic role of ET-1 and to discover new drugs, we sought to develop antagonists that inhibit the synthesis or the action of the peptide. We described the first orally active endothelin receptor antagonist (ERA) 5 years after the discovery of ET-1 and 3 years after the cloning and description of the two ET receptors (ET_A and ET_B)

(Arai et al. 1990; Sakurai et al. 1990), providing in addition the first evidence of a pathological role of endogenous ET-1 (Clozel et al. 1993). An extensive drug discovery program ensued, focused on developing ERAs with different profiles—selective antagonists for one of the two ET receptors or dual ET_A/ET_B receptor antagonists—so that the respective role of both receptors and differences in the potential efficacy and safety of these molecules could be well understood (Clozel et al. 1994, 1999; Iglarz et al. 2008). This research paved the way for new therapeutic opportunities for treating chronic diseases with unmet medical needs and where the ET system was clearly involved. Our research led us to choose dual ET_A/ET_B receptor antagonists for application in chronic cardiovascular diseases as these showed higher efficacy and better safety, particularly with regard to risk of fluid retention, than selective ET_A receptor antagonists in animal models (Mulder et al. 2000; Jasmin et al. 2001; Clozel and Flores 2006; Vercauteren et al. 2017). Bosentan became the first in class ERA to be approved for clinical use, and the first oral drug for the treatment of pulmonary arterial hypertension (PAH) (Clozel et al. 1994; Channick et al. 2001; Rubin et al. 2002), and then for the treatment of digital ulcerations in scleroderma (Korn et al. 2004; Matucci-Cerinic et al. 2011). Further research led to the development of macitentan, a more potent and once-daily dual ERA devoid of the bile salt transport inhibition and secondary increases in liver enzymes seen with bosentan (Fattinger et al. 2001; Treiber et al. 2014), and its registration for the treatment of PAH (Pulido et al. 2013). In the long-term phase 3 SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome) study in PAH patients (Pulido et al. 2013), and in phase 2 in systemic hypertension, rates of edema were similar between the placebo and macitentan-treated arms. This very good safety profile allowed a better escalation of dose compared with bosentan. Research efforts have since focused on aprocitentan, which we chose to develop in the treatment of resistant hypertension (Trensz et al. 2019), a form of hypertension that has a much more severe prognosis than classical essential hypertension (Daugherty et al. 2012). This paper reviews the scientific rationale for developing aprocitentan in forms of hypertension that cannot be well controlled with classical antihypertensive drugs.

Dual ERAs in essential hypertension

It is well recognized that the effects of ET-1 bear many similarities with the pathophysiology of hypertension, such as endothelial dysfunction, increased vascular tone, inflammation, fibrosis, tissue remodeling, and end-organ damage (Iglarz and Clozel 2010). Blockade of the ET receptors has demonstrated efficacy in decreasing blood pressure and preventing end-organ damage in animal models of hypertension (Li et al. 1994; Karam et al. 1996; Schiffrin 2001; Trensz et al. 2019). Among our molecules, the three dual, orally active ERAs—bosentan (Krum et al. 1998), macitentan (US Food and Drug Administration 2013), and more recently aprocitentan (Verweij et al. 2020)—have all been shown to significantly decrease blood pressure as monotherapy compared with placebo in essential hypertension trials.

Why resistant hypertension?

Despite there being a number of effective treatment options, approximately 10%–20% of the global population with hypertension is resistant to treatment (Carey et al. 2019; Noubiap et al. 2019), indicating that in these patients, the existing drugs are unable to tackle all the underlying pathological pathways involved in this form of hypertension. The American College of Cardiology and the American Heart Association define treatment-resistant hypertension as uncontrolled blood pressure ($\geq$130/80 mm Hg) despite concurrent use of at least three registered antihypertensive medications from different pharmacologic classes, including a diuretic, at optimal doses (Whelton et al. 2018). Currently approved antihypertensive therapies focus on the regulation of salt and water (diuretics), antagonism of the renin–angiotensin–aldosterone system (angiotensin-converting-enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs]), reduction of intracellular calcium overload (calcium channel blockers), sympatholytic activity (beta blockers, central alpha-agonist agents), and unselective vasodilators (Whelton et al. 2018; Williams et al. 2018). As no antihypertensive medications currently target the ET pathway, we speculate that in patients with difficult-to-control hypertension, the hypertension is "resistant" due, in part at least, to a dependence on ET.

This hypothesis is supported by the characteristics of resistant hypertension, in particular its frequent salt sensitivity, and by the observation that the known risk factors of resistant hypertension also are associated with ET-1 upregulation.

Resistant hypertension and its link with ET-1

The prognosis of patients with so-called resistant hypertension is more severe compared with those with nonresistant hypertension, with a much larger risk for target organ damage and cardiovascular morbidity and mortality (Daugherty et al. 2012; Kumbhani et al. 2013; Muntner et al. 2014). For example, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), participants with treatment-resistant hypertension had a 44%, 57%, 23%, 88%, 95%, and 30% higher risk of coronary heart disease, stroke, peripheral artery disease, heart failure, end-stage renal disease, and all-cause mortality, respectively, compared with participants without resistant hypertension during the almost 5-year duration of the study (Muntner et al. 2014).

Patients with resistant hypertension often have lower plasma renin activity, higher aldosterone and brain natriuretic peptide levels, and a salt-sensitive form of hypertension, compared with controls (normotensive subjects or subjects with hypertension controlled with $\leq$2 antihypertensive medications) (Gaddam et al. 2008). These patients in general respond well to aldosterone receptor blockade (Williams et al. 2015) but with certain safety concerns, such as hyperkalemia and renal insufficiency (Palmer 2004; Cooper et al. 2017).

All of these features suggest a role of ET-1, as plasma levels of ET-1 are elevated in low-renin models of hypertension, and plasma ET-1 and plasma renin activity are inversely cor-

related in hypertensive patients (Letizia et al. 1997; Schiffrin et al. 1997; Elijovich et al. 2001).

Salt sensitivity and ET-1

Salt-sensitive hypertension refers to the physiological trait by which the blood pressure of certain individuals exhibits changes parallel to changes in salt intake, while individuals without this trait are termed salt-resistant (Elijovich et al. 2016). Increasing evidence points toward ET-1 being a dominant factor in the pathogenesis of salt-sensitive hypertension. ET-1 production is dependent on salt intake; a high-salt diet, or an increased osmolality, increases ET-1 expression (Migas et al. 1995; Pollock and Pollock 2001; Tsai et al. 2006; Speed et al. 2015). Conversely, decreasing salt intake leads to a decrease in plasma ET-1 levels and correction of endothelial dysfunction in hypertensive patients (Ferri et al. 1998).

As a consequence of their upregulation by salt, ET-1 and potentially the other isoforms ET-2 and ET-3 play a major role in mediating the detrimental effects of salt, including hypervolemia, smooth muscle cell proliferation, and aldosterone release, thereby aggravating hypertension and its complications such as stroke, cardiac hypertrophy, and myocardial infarction (de Wardener and MacGregor 2002; Speed et al. 2015) (Fig. 1). Vascular endothelial cell ET-1 knockout mice on a high-salt diet have lower blood pressure compared with control mice on a high-salt diet (Speed et al. 2015). In addition, ERAs prevent hypertension and cardiac hypertrophy (Stasch et al. 1995) and blunt the increased contractile response of basilar arteries to a calcium channel activator (Salomone et al. 1996) in stroke-prone spontaneously hypertensive rats on a high-salt diet.

ET-1 itself perpetuates the salt sensitivity, as it perturbs salt homeostasis, promoting salt appetite and impairing the regulation of skin Na^+ storage (Speed et al. 2015, 2018). ET_B receptors are highly expressed in the subfornical organ (Hindmarch et al. 2008), where Na_x channels, the brain's sodium sensor for the regulation of salt intake (Noda 2006), are predominantly expressed (Watanabe et al. 2006). Accordingly, the sensitivity of Na_x to Na^+ is dose dependently upregulated by ETs (ET-3), through activation of ET_B receptors (Hiyama et al. 2013).

Risk factors for resistant hypertension and their link with ET-1

Certain populations are at a particularly high risk of developing resistant hypertension later in life; these include patients with a high body mass index (BMI), African Americans, postmenopausal women, and patients with obstructive sleep apnea (Coylewright et al. 2008; Roberie and Elliott 2012; Khan et al. 2013; Cohen 2017). Strikingly, all these risk factors represent situations compatible with high-ET status. In addition, diseases frequently associated with resistant hypertension, such as diabetes and chronic kidney disease, are also associated with an increased ET-1 production (Takahashi et al. 1990; Dhaun et al. 2012; Solini et al. 2014; Rossignol et al. 2015).

With regard to hypertension in patients with high BMI, a genetic polymorphism in the prepro-ET-1 gene, described as a G-to-T transversion that predicts a lysine/asparagine change in the protein, has been shown to be strongly associated with high BMI in the determination of blood pressure levels (Tiret et al. 1999). There was a much steeper increase of blood pressure with increasing BMI in carriers of the T allele than in GG homozygotes. As a consequence, the T allele was associated with an increase of blood pressure in overweight subjects (BMI $\geq$ 26 kg/m^2), while no significant effect was observed in lean subjects (Tiret et al. 1999). In isolated human mammary arteries, this GT/TT polymorphism was associated with an increased vascular reactivity to calcium and, with subthreshold concentrations of ET-1, a marked potentiation of phenylephrine-induced tone compared with the GG genotype (Iglarz et al. 2002). ET-1 levels were significantly increased in obese hypertensive patients compared with obese normotensive or lean hypertensive patients, and correlated with mean arterial blood pressure and left ventricular mass in patients with central obesity and hypertension (Parrinello et al. 1996).

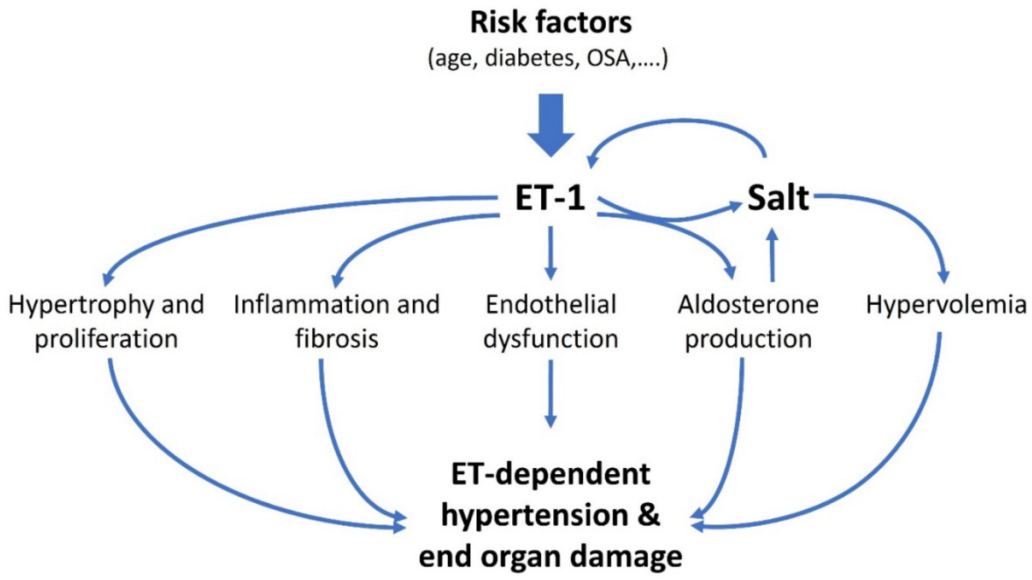
African American individuals present an increased sensitivity to high salt and develop more easily an increase in mean arterial blood pressure upon salt intake than White individuals (Luft et al. 1979). In hypertensive African Americans, plasma ET-1 concentrations are significantly higher than in normotensive African Americans, whereas the difference is much smaller between normotensive and hypertensive Caucasians (Ergul et al. 1996). These increased levels are accompanied by an increase in the endothelin-converting enzyme-1 activity and upregulation of the ET_B receptors in peripheral vasculature of African American hypertensive patients, which may contribute to the increased incidence of hypertension in this patient population (Grubbs et al. 2002).

A third risk factor of resistant hypertension is older age, particularly in women (Wenger et al. 2018; Carey et al. 2019). We know from animal models that elevated ET-1 levels and endothelial dysfunction are associated with aging (Barton et al. 1997). It has been further shown that, in humans, the difference (increase) in ET-1 levels between young (20–34 years) and middle-aged (35–59 years) subjects is greater in females than in males (Miyauchi et al. 1992).

Obstructive sleep apnea is associated with several cardiovascular comorbidities, with hypertension one of the most well-established cardiac risk factors associated with sleep apnea (Somers et al. 2008; Floras 2014). In patients with untreated obstructive sleep apnea, the apnea itself causes not only an increase in blood pressure but also an increase in plasma ET-1 levels (known to be increased in hypoxic conditions), both of which can be reversed following successful treatment with continuous positive airway pressure (Phillips et al. 1999).

The association of ET-1 with these aforementioned risk factors and the strong interaction between ET-1 and salt indicate an important role of ET-1 in difficult-to-treat forms of hypertension. Blocking the ET system with a dual ERA in these forms of hypertension thus potentially represents a new mode of action to reduce blood pressure and possibly prevent the complications of hypertension in these hypertensive patients.

Fig. 1. Role of ET-1 in mediating the effects of salt. ET-1, endothelin-1; OSA, obstructive sleep apnea.



Why aprocitentan?

Aprocitentan (*N*-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-sulfamide) is an orally active dual ERA that potently inhibits the binding of ET-1 to ET_A and ET_B receptors with an inhibitory potency ratio of 1:16, as determined by in vitro functional assays (Iglarz et al. 2008). Our preclinical data demonstrate that the mechanism of action of aprocitentan fits perfectly well with the pathophysiology of resistant hypertension, in contrast to drugs that interfere with the renin–angiotensin system (Trensz et al. 2019).

Aprocitentan efficacy in animal models of salt-dependent hypertension

Aprocitentan in monotherapy

Since vascular ET-1 expression is increased in animal models of salt-sensitive hypertension more than in models of spontaneous hypertension (SHR) (Larivière et al. 1993), the effect of aprocitentan was investigated in two different rodent models—a genetically induced model of hypertension in which rats developed SHR with normal renin levels and normal/reduced ET-1 expression and a model mimicking resistant hypertension in which rats developed hypertension with low renin and high salt (deoxycorticosterone acetate [DOCA]-salt rats) and overexpression of ET-1 (Trensz et al. 2019).

In both models, aprocitentan induced a dose-dependent and long-lasting decrease in mean arterial blood pressure, without any increase in heart rate. The hemodynamic effects were more pronounced in the DOCA-salt rats compared with the SHR ones, in line with the respective levels of ET-1 expression, showing that the higher the tissue ET-1 production is, the greater is the response to an ERA. The efficacy of aprocitentan in both models of hypertension is consistent with the work showing that inducible overexpression of human ET-1 in mice causes blood pressure elevation and vascular and renal injury, even in the absence of salt loading (Rautureau et al. 2015; Coelho et al. 2018). As expected, valsartan, a renin–angiotensin system blocker, also showed efficacy in the SHR model but, consistent with the poor response of low-renin patients to renin–angiotensin blockers, it was poorly effective at decreasing blood pressure in DOCA-salt rats.

In addition to hypertension, untreated DOCA-salt rats developed increased renal vascular resistance, left ventricular hypertrophy, and moderate cardiomyopathy. Chronic (28-day) administration of aprocitentan dose dependently decreased blood pressure but also decreased renal vascular resistance, left ventricular weight (not significantly), and the incidence of cardiomyopathy (Trensz et al. 2019).

Aprocitentan in combination therapy

The effect of aprocitentan in combination with renin–angiotensin system blockers (valsartan [an ARB] and enalapril [an ACEI]) on blood pressure and renal function was also investigated (Trensz et al. 2019). In both SHR and DOCA-salt rats, a single-dose combination of aprocitentan and valsartan led to a synergistic effect, as shown by the larger decline in blood pressure compared with the mere addition of both effects. The combination of aprocitentan and enalapril was also synergistic. In contrast, spironolactone (a mineralocorticoid receptor antagonist [MRA]), which acts downstream of ARBs or ACEIs, had only an additive effect when combined with valsartan or enalapril, and did not lead to any synergistic reduction in blood pressure. These data suggest a unique potential for combining an ERA with a renin–angiotensin system blocker.

When prescribed with ARBs or ACEIs, MRAs amplify the pharmacological blockade of the renin–angiotensin system and increase the risk of developing renal insufficiency and hyperkalemia, especially in patients with comorbidities (Palmer

2004; Lazich and Bakris 2014; Cooper et al. 2017). In contrast to combination of enalapril with spironolactone, combination with aprocitentan did not increase plasma urea or creatinine concentrations in hypertensive animals (SHR rats on a low-salt diet) for a similar blood pressure reduction (Fig. 2) (Trensz et al. 2019). These data demonstrate the benefits of blocking an alternative pathway to the renin–angiotensin system, rather than combining drugs tackling the same pathway.

Phase 2 trial of aprocitentan in essential hypertension

In patients with essential hypertension, aprocitentan in monotherapy demonstrated significant decreases in blood pressure, and a good safety profile, including lack of hepatoxicity and of excess edema (Verweij et al. 2020). In this randomized double-blind, dose-response study, patients with mild–moderate hypertension (mean trough diastolic blood pressure ≥90 to <110 mm Hg) entered a 4- to 6-week single-blind, placebo run-in period to eliminate the effects of any previous antihypertensive therapy and to ensure they were truly hypertensive. Patients ($N = 490$) were then randomized to receive aprocitentan 5, 10, 25, or 50 mg, placebo, or the ACEI lisinopril 20 mg as a positive control once daily for 8 weeks. This was followed by a 2-week single-blind placebo withdrawal period. Blood pressure was measured using unattended automated office blood pressure measurements for the primary endpoint—obtained at baseline, and at weeks 2, 4, and 8. This form of measurement is less variable than routine office blood pressure measurements due to a reduced white coat effect and provides a better estimate of blood pressure status (Myers et al. 2010; Muntner et al. 2019).

After 8 weeks of treatment, aprocitentan monotherapy lowered unattended automated blood pressure (as measured at trough) in a dose-dependent manner, with a plateau at 25 mg (Fig. 3); at 25 mg, the sitting blood pressure reduction (placebo corrected) was 9.9/7.0 mg Hg (systolic/diastolic). Lisinopril, at its prescribed dose of 20 mg, decreased sitting blood pressure by 4.8/3.8 mm Hg compared with the placebo. These absolute blood pressure reductions with aprocitentan at 8 weeks are in the ranges previously established as a surrogate for reduction in cardiovascular morbidity and mortality in patients with hypertension (Desai et al. 2006).

During the 8 weeks of treatment, aprocitentan was well tolerated across all four doses and no major safety signal was observed (Table 1). The study reported only four cases of mild–moderate peripheral edema (two each in the 25 and 50 mg groups), and no deaths and numerically fewer discontinuations due to adverse events (AEs) in the aprocitentan groups (ranging from 1.2% to 3.7%) than in the placebo group (6.1%), and 3.7% in the lisinopril group. The overall frequency of AEs was similar to those observed in the placebo group. Two cases of increased liver aminotransferases above three times the upper limit of the normal range were reported, one in the placebo group and one in the aprocitentan 5 mg group. There was an expected dose-dependent decrease from baseline to week 8 in hemoglobin concentration in the aprocitentan groups (ranging from 0.1 to 0.7 g/dL) compared with increases of 0.2 and 0.0 g/dL in the placebo and lisinopril groups, respectively. Aprocitentan dose dependently slightly increased the estimated plasma volume (25 mg vs. placebo: 6.9% vs. −0.3%, according to Strauss' formula [Strauss et al. 1951]), by vasodilation and volume redistribution, and decreased hematocrit, albumin, and uric acid, but there were no deleterious signs of fluid retention and little or no change in body weight.

Study of the effect of aprocitentan in subjects on high-salt diet

The impact of aprocitentan on body weight and fluid homeostasis was also investigated in healthy male subjects ($N = 28$) on a high-salt diet (Gueneau de Mussy et al. 2021). In this phase 1, randomized, double-blind, placebo-controlled, two-way crossover study, three doses of aprocitentan (10, 25, and 50 mg/day for 9 days) were compared with a placebo. The study design was similar to that previously used to investigate fluid retention induced by avosentan, a selective ET_A receptor antagonist in healthy subjects on a high-salt diet (Smolander et al. 2009).

Aprocitentan induced a moderate (i.e., less than 1 kg) but significant increase in body weight (the primary endpoint), at doses between 10 and 50 mg (Fig. 4) (Gueneau de Mussy et al. 2021). Aprocitentan induced a dose-dependent decrease in hemoglobin and minimal decrease in hematocrit, signs of hemodilution. However, no signs of marked sodium retention or edema were observed with aprocitentan at the highest dose of 50 mg. This is likely due to a more balanced blockade of both ET_A and ET_B receptors with aprocitentan than with selective ET_A receptor antagonists, preventing ET-1 from activating ET_B receptors, which are known to trigger vascular leakage via nitric oxide and vascular endothelial growth factor release (Vercauteren et al. 2017). Strikingly, at 50 mg, despite almost a 1 kg increase in body weight, an increased urinary excretion of sodium was reported (Fig. 4), as well as a decrease in plasma aldosterone and copeptin levels. This is in marked contrast to the profile of the selective ET_A receptor antagonist avosentan in a prior study, which caused significant, dose-dependent sodium and water retention after repeated administration (Smolander et al. 2009).

Phase 3 trial of aprocitentan in resistant hypertension

Based on the totality of the data, a large phase 3 study has been initiated to assess the efficacy and durability of the effect of aprocitentan in patients with resistant hypertension (Danaietash et al. 2022). PRECISION (PaRallEl-group, phase 3 study with aproCItentan in Subjects with ResIstant HypertensiON) is a multicenter, blinded, randomized study (clinicaltrials.gov: NCT03541174). It is designed to evaluate both the efficacy and the durability of effect, as well as the safety and tolerability, of aprocitentan in patients with "true" resistant hypertension when added on top of guideline-recommended antihypertensive medications, including a diuretic (Carey et al. 2018; Williams et al. 2018).

The primary objective is to demonstrate the blood-pressure-lowering effect of aprocitentan added to the stan-

Fig. 2. Effect of the combination of chronic treatment of aprocitentan or spironolactone with a renin–angiotensin system blocker on blood pressure, plasma creatinine, and plasma urea in sodium-depleted SHR rats. Effect of 11-day oral administration of the vehicle ($n = 4$) or 6-day oral administration of enalapril 10 mg/kg per day ($n = 19$), followed by 5-day oral administration of either enalapril 10 mg/kg per day plus aprocitentan 10 mg/kg per day ($n = 9$) or enalapril 10 mg/kg per day plus spironolactone 300 mg/kg per day ($n = 10$) combinations, on mean arterial pressure (*a*), plasma creatinine (*b*), and plasma urea (*c*) in sodium-depleted spontaneously hypertensive rats. Data are presented as mean ± SEM; ****$P < 0.0001$ between groups. For a similar blood pressure reduction (*a*), the combination of aprocitentan with enalapril, unlike the combination of spironolactone with enalapril, does not induce renal insufficiency as measured by plasma creatinine (*b*) and urea (*c*). Reproduced with permission under the Creative Commons Attribution License 4.0 (CC BY; https://creativecommons.org/licenses/by/4.0/) from Trensz et al. (2019).

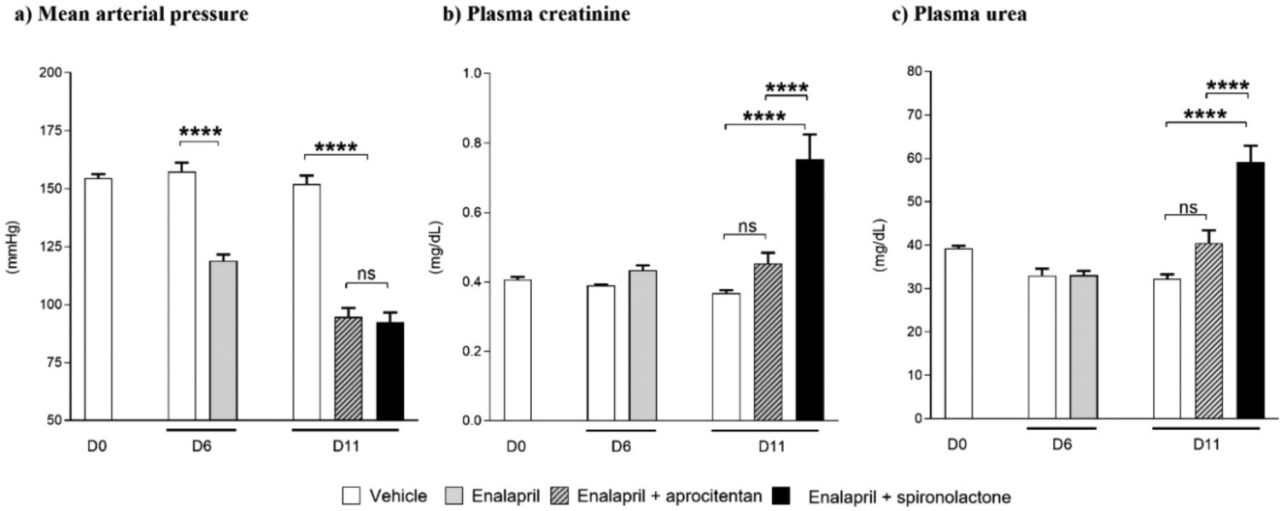
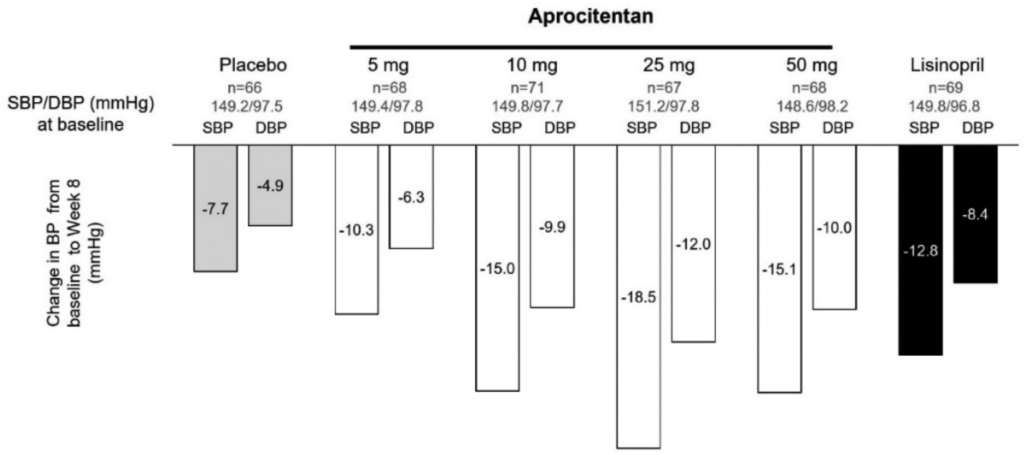


Fig. 3. Change in blood pressure with aprocitentan over 8 weeks in participants with essential hypertension. Mean change from baseline to week 8 in systolic and diastolic blood pressure measured using automated (unattended) office blood pressure measurement in the dose-finding phase 2 study with aprocitentan in participants with essential hypertension. DBP, diastolic blood pressure; SBP, systolic blood pressure. Data extracted from Verweij et al. (2020).



dard of care after 4 weeks of double-blind treatment and the key secondary objective is to demonstrate that the effect on blood pressure is sustained after 32 weeks of treatment with aprocitentan, by showing a return to higher blood pressure levels after treatment cessation (Danaietash et al. 2022). Blood pressure is assessed by measurement of unattended automated office blood pressure. The study will also evaluate the long-term safety and tolerability of aprocitentan during 48 weeks of treatment. In addition, plasma biomarkers that reflect the activity of the ET system will be measured to compare levels in patients with "true" resistant hypertension versus patients whose blood pressure is controlled.

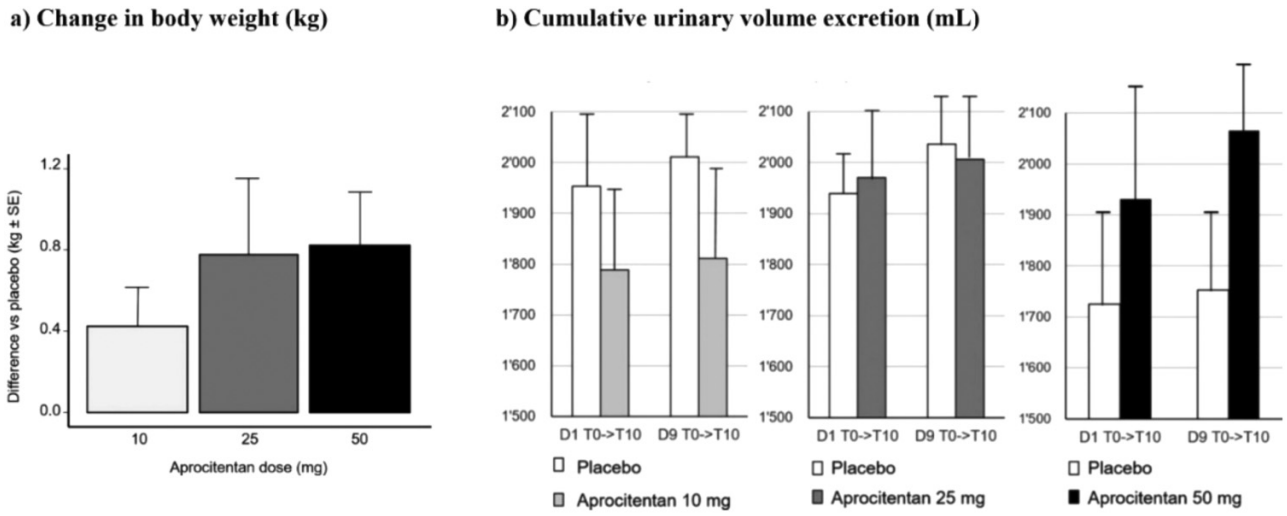
A strength of the study is the long screening/run-in period of at least 8 weeks—this is to enable the confirmation of a "true" resistant hypertension diagnosis, overcoming a frequent methodological limitation of studies that results in

Table 1. Summary of AEs reported with aprocitentan in participants with essential hypertension.

		Aprocitentan				
	Placebo ($n = 82$)	5 mg $n = 82$	10 mg $n = 82$	25 mg $n = 82$	50 mg $n = 81$	Lisinopril($n = 81$)
Patients with ≥1 AE	30 (36.6)	18 (22.0)	24 (29.3)	33 (40.2)	22 (27.2)	26 (32.1)
Patients with ≥1 serious AE	0	0	0	2 (2.4)	0	1 (1.2)
AE leading to treatment discontinuation	5 (6.1)	1 (1.2)	2 (2.4)	3 (3.7)	3 (3.7)	3 (3.7)
Deaths	0	0	0	0	0	0
Most frequent AEs						
Hypertension	4 (4.9)	1 (1.2)	0	2 (2.4)	3 (3.7)	3 (3.7)
Headache	1 (1.2)	1 (1.2)	2 (2.4)	2 (2.4)	2 (2.5)	4 (5.0)
Nasopharyngitis	1 (1.2)	1 (1.2)	2 (2.4)	2 (2.4)	0	4 (5.0)
Upper respiratory tract infection	1 (1.2)	0	4 (4.9)	1 (1.2)	2 (2.5)	1 (1.2)
Arthralgia	2 (2.4)	0	1 (1.2)	1 (1.2)	3 (3.7)	0
Dizziness	1 (1.2)	1 (1.2)	1 (1.2)	1 (1.2)	0	1 (1.2)
Pain in extremity	1 (1.2)	1 (1.2)	0	1 (1.2)	2 (2.5)	0

Note: Data are presented as *n* (%). Incidence of AEs reported in the 8-week dose-finding phase 2 study with aprocitentan in patients with essential hypertension. Reproduced from Verweij et al. 2020.

Fig. 4. Change in body weight and urinary volume excretion with aprocitentan in healthy normotensive subjects on a high sodium diet. (*a*) Placebo-corrected changes (mean ± SE) from baseline to day 9 in body weight and (*b*) mean cumulative 10 h urinary volume excretion (mL; ±SE) on days 1 and 9, in healthy normotensive subjects on a high-sodium diet after administration of 10, 25, and 50 mg aprocitentan. Reproduced with permission under the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0; https://creativecommons.org/licenses/by-nc-nd/4.0/) from Gueneau de Mussy et al. (2021).



the inclusion of patients who do not have "true" resistant hypertension. The study begins with a run-in period where all eligible patients with a sitting systolic blood pressure of ≥140 mm Hg despite three or more antihypertensive medications for at least 1 year will be switched to standardized background antihypertensive therapy, provided as a single pill, for at least 4 weeks before entering a 4-week single-blind run-in period where a placebo is added to the background antihypertensive therapy. The standardized background therapy consists of a fixed combination of a calcium channel blocker (amlodipine), an ARB (valsartan), and a diuretic (hydrochlorothiazide), available at two dose strengths (5/160/25 and 10/160/25 mg). The treatment period consists of three sequential parts. Part 1 is a 4-week double-blind, parallel-group, and placebo-controlled period where patients are randomized (1:1:1) to aprocitentan 12.5 or 25 mg or a placebo and is designed to demonstrate the blood-pressure-lowering effect of aprocitentan. These two doses of aprocitentan were selected based on the results of the phase 2 dose-finding study (Verweij et al. 2020). Part 2 is a 32-week single-blind and single-arm period where all patients receive aprocitentan 25 mg and is followed by a 12-week double-blind, randomized, parallel-group, and placebo-controlled withdrawal period where patients are rerandomized to aprocitentan 25 mg or placebo (1:1) (part 3). Parts 2 and 3 are intended to demonstrate the persistence of effect of aprocitentan. The safety follow-up period covers the 30 days after the last dose of study treatment.

Enrollment into the PRECISION study began in June 2018 and was completed in January 2021. The study was conducted at 193 sites in 22 countries, with a total of 730 patients randomized. At the time of writing this article, results were not available (expected mid-2022).

Conclusion

Given the associated cardiovascular risks and difficulty in managing patients with resistant hypertension, there is a major medical need for additional pharmacological therapy acting on a pathway different from those currently used, targeting the etiology of these difficult-to-treat forms of hypertension, and one that can be combined with existing therapies. Indeed, it has been over 30 years since an antihypertensive drug working via a new pharmacological pathway was brought to the market. Aprocitentan, an oral, once-daily, dual ET_A and ET_B ERA, has a mechanism of action that is ideally suited for the pathophysiology of these difficult-to-treat forms of hypertension, distinct from other agents for the treatment of hypertension, and is not expected to cause hyperkalemia or renal failure. With its efficacy and promising safety profile suggested in its development up to now, aprocitentan, particularly in combination with other drugs, including diuretics, may have a promising future in patients at risk of difficult-to-treat hypertension and we eagerly await the results of the phase 3 PRECISION study in patients with true resistant hypertension.

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MC is a full-time employee of Idorsia Pharmaceuticals, receives stock or stock options in Idorsia, and is a shareholder in Idorsia Pharmaceuticals.

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