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ANTIHYPERTENSIVE AGENTS: MECHANISMS OF DRUG ACTION (ME ERNST, SECTION EDITOR)

Update on Endothelin Receptor Antagonists in Hypertension

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Abstract

Purpose of Review To review the most recent data on the development of endothelin receptor antagonists (ERAs) for the treatment of hypertension and the management of diabetic nephropathy

Recent Findings Recent reviews and meta-analyses of experimental and clinical data obtained with ERAs confirmed that endothelin receptor blockade is associated with significant decreases in blood pressure in essential hypertension but also in resistant hypertension. In addition, in patients with diabetic nephropathy, ERAs induce significant 30–40% decreases in albuminuria when administered on top of blockers of the renin-angiotensin system. Yet, the benefits of ERAs have often been limited by their tolerability profile, essentially fluid retention and the development of edema and liver toxicity. Hence, several programs have been interrupted. Today, only one ERA, aprocitentan, is still under development for the treatment of resistant hypertension. Regarding the place of ERAs in the management of diabetic nephropathy, the results of the SONAR trial with atrasentan are eagerly awaited but the recent interruption of this trial because of insufficient events is worrisome, as one might not obtain all the expected information for this major trial.

Summary Blockade of endothelin receptor have a high potential in the treatment of hypertension and the prevention of the progression of renal diseases such as diabetic nephropathy. Today, the number of clinical programs investigating the potential benefits of ERAs is limited and more data must be obtained to define the real place of ERAs in these indications.

Keywords Antagonists · Experimental hypertension · Resistant hypertension · Renal · Proteinuria

Introduction

In 1988, Yanagisawa et al. discovered the endothelin system [1]. The demonstration that endothelin-1 (ET-1), produced by endothelial cells, induces a potent and long-lasting vasoconstriction in mammalian vessels including human veins and arteries has contributed to our actual understanding of the importance of the endothelin system in the regulation of vascular tone and hence blood pressure (BP) control and perfusion of every organ of the body. Since the original report by Yanagisawa, thousands of papers have been published revealing the complexity of the endothelin system, ET-1 and its receptors being present ubiquitously in tissues and with different functions in each of them (for more information see the excellent review by Davenport et al. [2••]) (Table 1). Considering the potential interests of blocking the endothelin system in cardiovascular diseases such as hypertension, heart failure, or pulmonary hypertension, one important development has been the identification and characterization of the ET_A and ET_B endothelin receptors based on their molecular structures but also based on their pharmacological responses to various agonists and antagonists [3]. These two receptors are widely distributed in the body and present in many tissues. The ratio of the density of ET_A and ET_B receptors is organ-dependent. Thus, in humans, the brain and kidneys contain more ET_B than ET_A receptors whereas ET_A receptors predominate in all vessels including renal vessels [2••]. This aspect may be determinant to interpret organ-specific responses to endothelin receptor antagonists (ERA). In the cardiovascular system, endothelin receptors have very distinct and contrasting effects. ET_A receptors activation induces a vasoconstrictor response in large conduit arteries as well as in small resistance vessels, thus contributing to maintain the basal vascular tone.

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Table 1 Main distribution and function of endothelin receptors throughout the human body

Organ	Cell type	ET_A receptor density	ET_B receptor density	Function
Vasculature	Endothelial cells	+++	+	Vasoconstriction (ET_A), vasodilation (ET_B)
	Smooth muscle cells	+++	+	Constriction (ET_A), growth and proliferation Increase oxidative stress
Heart	Atrial myocytes	+++	+	Positive inotropic effect, positive chronotropic effect, increase atrial natriuretic peptide secretion
	Ventricular myocytes	+++	+	Positive inotropic effect; stimulate hypertrophy
Lung	Vasculature	++++	++	Vasoconstriction, smooth muscle proliferation
	Airway smooth muscle cells	+	+++	Contraction, proliferation
	Epithelial cells	++	+	Cilia beating rate, mediator release, water transport
	Alveolar wall tissue	++	++	Increased surfactant production
Kidney	Vascular cells	+++	++	Increase medullary blood flow (ET_B), constriction of efferent arteriole, regulation of glomerular filtration rate
	Epithelial cells (collecting duct essentially)	+	+++	Natriuretic and diuretic effects, inhibition of Na/K ATPase Inhibition of vasopressin effects
Brain	Cerebral cortex (neurons and glial cells	++	+++	Increase of blood brain barrier permeability, inflammation, excitotoxicity, impairment of fast axonal transport, and astrogliosis
	Cerebral vasculature	+++	+	Vasoconstriction, regulation of flow, and vascular permeability
Liver	Endothelial cells	+++	+	Vasoconstriction, inflammation, fibrosis, sinusoidal relaxation, portal vein vasoconstriction
	Hepatic cells	++	++	Stellate cell constriction in the sinusoid
	Kupffer cells		+	
Eye	Vascular and retinal cells	+++	?	Blood flow control, regulation of retinal hemodynamics
Ovaries	Granulosa and theca cells	++	+	Ovarian follicle development, steroidogenesis

NB: Endothelin receptors are also present in the pituitary gland, adrenal and thyroid glands, the gastro-intestinal tract, the skin, the bone marrow, and the adipose tissue (see [2])

In contrast, activation of vascular ET_B receptors produces a vasodilator response due to the release of endothelial factors such as nitric oxide or prostacyclin. ET_B receptors also participate in the clearance of ET-1 [4]. Thereby, ET_B receptors tend to counterbalance the vascular effects of ET_A receptors but, in pathological conditions, this opposing effect may be altered, a reason why in some circumstances, non-selective blockade of both ET_A and ET_B receptors may be more advantageous than selective ET_A receptor blockade [5].

Endothelin and Hypertension

Experimental Data

Because of its important role in the regulation of vascular tone, it is reasonable to think that the endothelin system contributes to the pathogenesis of some forms of hypertension and today, several lines of evidence would support this hypothesis. Evidence have been gathered essentially from experimental studies using transgenic murine models, in which a component of the endothelin system was either knockdown or overexpressed in tissue or cells of interest, because whole body knock-outs of ET-1, ET_A, and AT_B receptors as well as endothelin-converting enzyme result in a lethal phenotype. When considering BP only, these models have provided some surprising results. Thus, the overexpression of ET-1 has resulted in either no change, slight increases, and decreases in BP. Recently, Lu et al. [6] have performed a meta-analysis of all experimental studies in which ET-1 was overexpressed. They concluded that global ET-1 overexpression in mice lowers, rather than increases, BP and this, in an age-dependent manner [6]. Of note, when ET-1 was overexpressed in the endothelium only, BP was significantly higher in transgenic mice than in wild type mice [7]. In accordance with this observation, a reduced expression of ET-1 resulting in lower systemic ET-1 levels down to 35% of that in wild type animals caused hypertension [8]. Of note, selective knock-out of ET-1 in the collecting tubule of the nephron was associated with a higher BP and the development of salt-sensitive hypertension [2••]. A similar blood pressure phenotype was obtained with the deletion of ET_A or ET_B receptors in collecting duct cells suggesting the important role of the epithelial

sodium channel (ENaC) in the development of salt-sensitive hypertension due to alterations of the endothelin system. In non-transgenic animals, elevated ET-1 production was found in several salt-sensitive models of hypertension such as the DOCA-salt rat, the Dahl salt-sensitive rat, and rodent models of malignant hypertension [9]. In these models, high ET-1 levels were associated with significant decreases in BP upon administration of selective ET_A or mixed ET_A/ET_B receptor antagonists.

Clinical Data

Clinical studies have also provided useful information on the role of endothelin in hypertension. Elevated plasma ET-1 levels have been measured in patients with essential hypertension but this observation has not always been consistent [2••]. Hypertensive patients of African-American origin and patients with severe hypertension appear to have higher plasma ET-1 levels [10], a finding which would corroborate the role of the endothelin system in salt-sensitive hypertension as discussed above. In several clinical studies and trials, the BP-lowering effect of ERA was measured using either office or 24-h ambulatory BP monitoring. These studies included patients with moderate essential hypertension, hypertension associated with chronic heart failure, or diabetic nephropathy and more recently resistant hypertension as will be discussed below. In all situations, the administration of ERAs was associated with significant decreases in BP. In hypertensive patients with chronic kidney diseases (CKD), Dhaun et al. have also shown that ERA can restore a normal circadian rhythm of BP [11•]. This effect may be favorable to retard the progression of renal diseases.

The impact of endothelin receptor antagonists on BP has been reviewed in a recent meta-analysis, in which all studies involving hypertensive patients were considered (except pulmonary hypertension) [12••]. The meta-analysis contained 18 trials including 4898 patients. Studies were conducted with selective ET_A and dual ET_A/ET_B ERA such as atrasentan, avosentan, bosentan, darusentan, and tezosentan. Seven of these trials also assessed the impact on mortality. Neither a decrease nor an increase in mortality was found in this analysis. However, the results indicating that endothelin antagonists are safe in this respect should be considered with caution because of the small number of studies and patients. Regarding BP, ERA induced significant decreases in sitting office systolic and diastolic BP as well as significant decreases in 24-h systolic (Fig. 1) and diastolic BP when compared to placebo. The mean decreases in systolic and diastolic BP at the office were −6.12 and −3.81 mmHg, and the changes in 24-h ambulatory systolic and diastolic BP were respectively −7.65 and −5.92 mmHg. There was no difference in antihypertensive efficacy between selective and non-selective antagonists in this analysis. In contrast, there was no significant change in heart rate. This meta-analysis also assessed the incidence of severe adverse events. The rate of severe adverse events (including cardiovascular events, acute pulmonary edema, dyspnea, severe allergies, and severe liver dysfunction) was significantly higher in the group treated with ERA than with placebo ($n = 3404$ patients, RR 1.34; 95% CI 1.13–1.60).

Taken together, these results confirm that blockade of the endothelin system has a favorable impact on BP in several clinical situations. However, as will be discussed below, the potential benefits of lowering BP with ERA must be balanced with the risk of developing side effects.

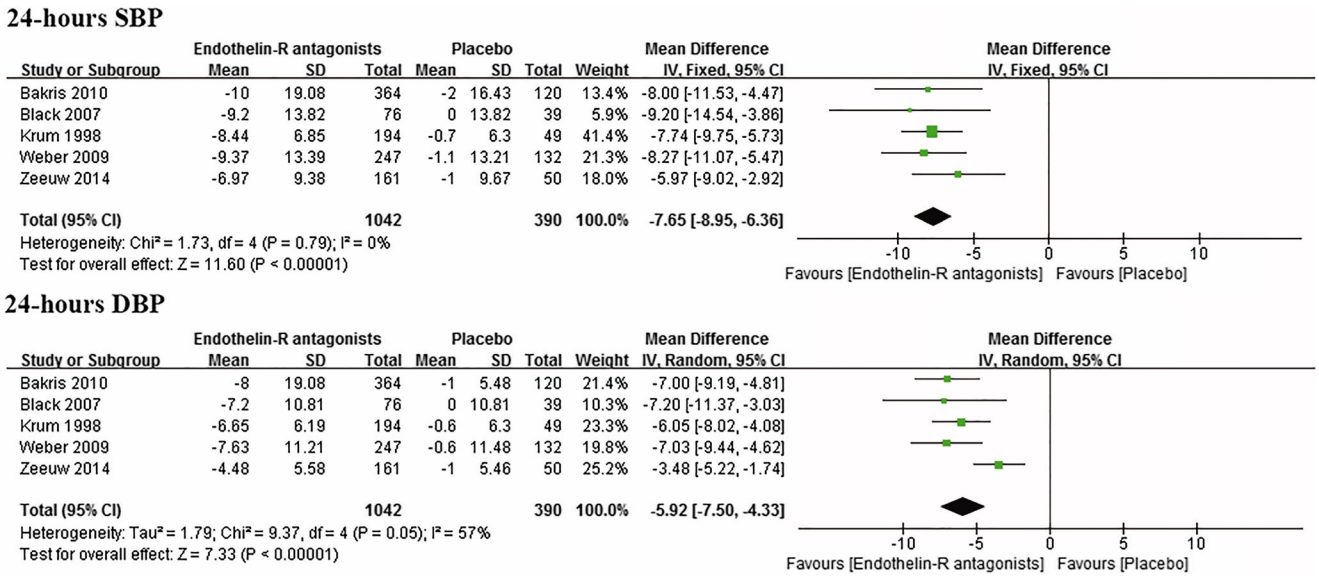


Fig. 1 Effects of endothelin receptor antagonists on systolic and diastolic ambulatory blood pressure versus placebo (from ref. 12)

Endothelin Receptor Antagonists: New Developments

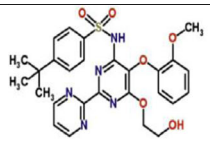
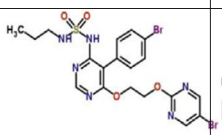
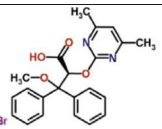
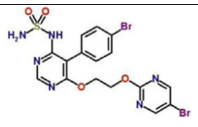
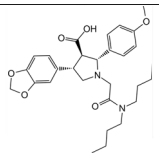
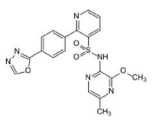
Numerous selective and non-selective agonists and antagonists of ETA and ETB receptors have been developed for research as well as for clinical purposes since the development of bosentan (for review of the chemical development, see Boss et al. [13]). Today, three endothelin receptor antagonists are on the market to treat pulmonary hypertension (bosentan, macitentan, and ambrisentan). Atrasentan is studied in patients with type 2 diabetes and diabetic nephropathy, and a study with zibotentan, a selective ET_A receptor antagonist, is conducted by the London University College, in patients with renal disease due to scleroderma (Zibotentan Better Renal Scleroderma Outcome Study (ZEBRA) (NCT02047708). Sparsentan, an orally active, dual-acting angiotensin type 1 receptor blocker and highly selective ETA receptor antagonist, is also under investigation for the treatment of primary focal segmental glomerulosclerosis (FSGS) [14]. Only one new endothelin receptor antagonist is still investigated for the treatment of hypertension, i.e., aprocitentan, the active metabolite of macitentan. Table 2 summarizes the pharmacological characteristics of these endothelin antagonists.

Endothelin Receptor Antagonists and Resistant Hypertension

The first study demonstrating the ability of an endothelin receptor antagonist to lower BP in hypertensive patients was done with bosentan (2000 mg/d) in 293 patients with moderate essential hypertension [15]. In this 4-week placebo-controlled randomized double-blind study, bosentan was superior to placebo and as effective as enalapril (20 mg/day) to decrease diastolic BP, the pre-defined primary end point. However, the incidence of side effects was significantly higher than in the other groups with more headache, flushing, leg edema, and liver injury. The second large study was done with darusentan in patients with moderate essential hypertension [16]. In this dose-response double-blind placebo-controlled study, increasing doses of darusentan produced dose-dependent reductions in both systolic and diastolic BP. As expected, the incidence of side effects increased dose-dependently as well, with headaches and fluid retention being the commonly reported complains. Because of the relatively unfavorable balance between the antihypertensive efficacy and the risk of side effects in a population of hypertensive patients largely asymptomatic at baseline, research on the potential usefulness of ERA in hypertension was switched to resistant hypertension.

In resistant hypertension, two major studies were performed with darusentan. The first was the so-called DORADO trial, a randomized, double-blind study in which 379 patients with systolic BP of 140 mmHg or more (≥ 130 mmHg if patient had diabetes or chronic kidney disease) receiving at least three BP-lowering drugs, including a diuretic, at full or maximum tolerated doses, were enrolled [17]. The second one was also realized with darusentan using a similar protocol but with an active control group receiving guanfacin 1 mg/day, a central α-2 adrenoceptor agonist [18]. In this latter study, both office and 24-h ambulatory BP were measured. In the first study, a

Table 2 Pharmacological characteristics of endothelin receptor antagonists on the market or still under investigations. PAH pulmonary arterial hypertension

	Bosentan (Tracleer®)	Macitentan (Opsumit®)	Ambrisentan (Letairis®, Volibris®)	Aprocitentan (ACT-132577)	Atrasentan	Zibotentan
Structure						
Official or target indication	PAH	PAH	PAH	Resistant hypertension	Diabetic nephropathy	Sclerodermia
Time to max concentration (hours)	3-5	4-12	1.7-3.3	30	0.8	1
Terminal half life (hours)	5.4	16	15	40.2-65.6	26.4	8.17
Excretion in urine (%)	<3%	50%	low	Not detected	<10%	93
ET_A selectivity	20	782	616	61	>1000	>1000

significant additional decrease in BP was obtained in patients with resistant hypertension after addition of darusentan reflecting the efficacy of endothelin receptor blockade in this clinical situation. However, in the second study, placebo and darusentan were not significantly different at 14 weeks based on the primary end points, i.e., sitting office BP. However, when changes in BP were assessed using 24-h ambulatory BP monitoring, darusentan was clearly superior to placebo and guanfacin in lowering BP in these resistant patients. Unfortunately, as the pre-specified co-primary end points were not reached, the manufacturer had no other choice than to put the project on hold. This was very disappointing since the major issue was the method used to measure BP and not the efficacy of the ERA as discussed in an interesting editorial [19].

Today, the only ongoing studies in hypertension with the objective to demonstrate a clinical benefit for patients with resistant hypertension are done with aprocitentan, the active metabolite of macitentan. Aprocitentan (ACT-132577) is an orally active dual ERA. Aprocitentan has a lower potency, but reaches higher plasma concentrations and has a longer half-life than macitentan [20] (cf Table 2). In a phase 2 study, the efficacy, safety, and tolerability of aprocitentan were evaluated in patients with essential hypertension. In this study, 490 patients with essential hypertension were randomized to receive either aprocitentan 5, 10, 25, and 50 mg, or placebo, or lisinopril 20 mg once daily. The results showed a mean reduction from baseline in diastolic BP between 6.3 and 12.0 mmHg in a statistically significant dose-dependent manner for the aprocitentan groups versus a decrease of 4.9 mmHg in the placebo group and a decrease of 8.4 mmHg in the lisinopril group. Systolic BP reductions ranged from 10.3 to 18.5 mmHg in the aprocitentan groups and were 7.7 and 12.8 mmHg in the placebo and lisinopril groups (data taken from www.idorsia.com/documents/com/fact-sheets-presentations/fs-clinical-development.pdf, last visit April 4th 2018). Aprocitentan was well tolerated across all four doses in this patient population. Discontinuation from study treatment due to an adverse event ranged between 1.2 and 3.7% for the aprocitentan groups versus 6.1% in the placebo group and 3.7% in the lisinopril group. Peripheral edema and weight gains were observed in few cases receiving the highest doses of aprocitentan. These encouraging results suggest that aprocitentan may be a good new candidate for the management of patients with resistant hypertension with a very acceptable tolerability profile. Therefore, a phase III study in patients with resistant hypertension is now in preparation.

Endothelin Receptor Antagonists, Hypertension, and Kidney Diseases

Besides regulating the systemic vascular tone, endothelin has important intrarenal actions, which may contribute to the development of hypertension and renal disease progression. These include an ET_A receptor-mediated increase in renal vascular resistance, the generation of reactive oxygen species, and the promotion of renal inflammation [21, 22]. These may lead to podocyte injury, mesangial proliferation, matrix accumulation, glomerulosclerosis, and renal fibrosis. In addition, ET_A receptor activation increases T cell infiltration in the renal cortex in mice and in vitro studies recently demonstrated that ET_A receptor activation enhances CD4+ T cell production of IL-17, a mechanism implicated in the pathogenesis of hypertension [23].

In line with these experimental observations, many experimental and clinical studies have been dedicated to the exploration of the potential benefits of endothelin receptor blockade in animal models as well as in patients with diabetic and non-diabetic nephropathies. In animal models, ET_A receptor blockade had several favorable renal effects including a reduction of albumin permeability leading to a decreased urinary albumin excretion and decreases in inflammatory markers and podocyte loss (for review see Anguiano et al. [24]).

Several phases 2 and phase 3 studies have been conducted in patients with diabetic nephropathy with or without hypertension in order to assess mainly the ability of ERA to lower proteinuria and/or BP [24]. Studies were done using bosentan, a mixed ET_A/ET_B antagonist; avosentan, a selective ET_A antagonist; and atrasentan, another selective ET_A receptor antagonist. All studies performed with avosentan [25, 26] and atrasentan [27–29] reported a significant reduction in urinary albumin excretion of up to 40% when compared to placebo or standard therapy. Interestingly, this reduction of albuminuria occurred in patients already treated with an optimal dose of a blocker of the renin-angiotensin system and was partially independent of the decrease in BP. Yet, in the study performed by Andress et al., no statistically significant differences in inflammation markers (CRP, IL-6, and TGFβ) were found between the ERA and the placebo groups [28].

Today, only one large phase 3 trial is under way with atrasentan, the SONAR (Study Of diabetic Nephropathy with AtRasentan) trial [30]. This multicenter study is designed to include more than 4000 patients with diabetic nephropathy and albuminuria and a glomerular filtration rate between 45 and 90 ml/min/1.73 m^2 (CKD stages 2 to 4), and with a follow-up of 2 years. It will compare the effect of atrasentan at a low dose of 0.75 mg/day versus placebo on albuminuria and long-term effects on renal function and cardiovascular events. The trial will therefore investigate whether it is possible to reduce the renal risk without increasing the risk of heart failure.

The results of SONAR are expected with great interest because they may determine the future of ERA in diabetic nephropathy. Unfortunately, AbbVie, the promoter of the project, has recently announced the premature closure of this trial (see https://news.abbvie.com/news/media-

statements/abbvie-statement-on-sonar-study-closure.htm). The motivation given by the sponsor to explain this early interruption is that "the ongoing monitoring of renal events observed in the study has revealed considerably fewer end points than expected by this time, which will likely affect the ability to test the SONAR study hypothesis. Therefore, AbbVie has determined that it cannot justify continuing the participation of patients in the study. The decision to close the SONAR study early was not related to any safety concerns." At this stage, whether the data of SONAR will provide valid and statistically relevant information to conclude on the renal and cardiovascular benefits of atrasentan in diabetic nephropathy remain uncertain.

Tolerability Profile of Endothelin Receptor Antagonists: a Real Issue?

The clinical development of ERA has been impaired by the relatively high incidence of side effects among which fluid retention leading to weight gain, peripheral edema, and sometime acute congestive heart failure are definitively the most frequent. A systematic review and meta-analysis of the clinical adverse effects induced by endothelin receptor antagonists in trials have been published recently [31••]. This meta-analysis covered mainly the incidence of abnormal liver tests, peripheral edema, and the occurrence of anemia.

Fluid retention induced by endothelin receptor antagonists is undoubtedly the most critical and discussed issue. The mechanisms of this side effect remain partially understood and combine probably a sodium and water retention with a vascular extravasation resulting in a fluid redistribution within the body. Weight gain and peripheral edema have been reported with all ERA but the incidence varies between antagonists. For example, macitentan has been associated with a lower incidence of peripheral edema in patients with pulmonary hypertension, and there was no difference in incidence when compared to the control groups in the meta-analysis [31••]. The major determinants for the development of fluid retention are the dose of the endothelin antagonist and to a certain degree the selectivity of the antagonist, although peripheral edema occurred even with highly selective ET_A receptor antagonists. In clinical trials, confounding factors may be the use of diuretic, the level of subjects' salt intake and the patient's selection, patients with advanced renal diseases, or pre-existing congestive heart failure being at higher risk of developing fluid overload. Today, the main question is whether fluid retention should be a true limitation to the use of ERAs, for example in patients with resistant hypertension or diabetic nephropathy. Indeed, many investigators have reported that ERA-induced fluid overload is very sensitive to diuretic therapy and rapidly reversible; hence, fluid retention could be managed easily with the prescription of a diuretic or an adaptation of diuretic doses. In any case, patients should carefully follow their body weight, and prescribers should pay more attention to the selection of patients, avoiding patients at high risk of fluid overload.

Regarding the development of hepatic toxicity, a less common side effect of endothelin antagonists, a recent meta-analysis has shown that the risk of developing abnormal hepatic tests is increased 2.98-fold with this class of agents. However, this side effect appears to occur mainly with bosentan and sitaxentan [32].

Conclusions

Selective and mixed endothelin receptor antagonists lower BP and/or albuminuria and may be useful to improve BP control in patients with essential hypertension, resistant hypertension, and hypertension associated with diabetic nephropathy. The major challenge today is how to valorize these clinical benefits limiting the occurrence of side effects. New ERA appear to be devoid of liver toxicity solving this issue. Regarding the fluid overload, one solution is perhaps in the use of lower doses as the tolerability profile appears to be dose-dependent. Combining endothelin antagonists with a diuretic may be another way to circumvent the problems of fluid retention.

Presently, there is still no strong evidence that the use of ERAs has a positive impact on major cardiovascular and renal end points in patients with essential hypertension and/or diabetic nephropathy. Therefore, there is an important need for additional studies providing this crucial information. In the field of resistant hypertension, there is still room for the development of new effective drugs enabling to improve BP control beyond diuretics, calcium antagonists, and blockers of the renin-angiotensin system. In the field of diabetic nephropathy, however, ERAs will be confronted to serious competitors such as inhibitors of sodium-glucose co-transporter 2 (SGLT2) or glucagon-like peptide-1 receptor agonists, for which there is now good evidence that they lower cardiovascular mortality [33, 34] and renal end points [34] in type 2 diabetes.

Compliance with Ethical Standards

Conflict of Interest MB has received research grants from Actelion AG, Switzerland, and Speedel AG, Switzerland.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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