

Role of Angiotensin-1-Receptor Blockers In Cardiorenal Disease

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Abstract: Arterial hypertension is one of the most important risk factors for cardiovascular disease. Angiotensin-1-receptor blockers (ARB) are a class of drugs that potently inhibit the vasoconstriction and other vascular effects of angiotensin including proliferation of vascular smooth muscle cells by selective binding to the AT1-receptor. The present review summarizes the most relevant experimental and clinical data on this new class of drugs.

ARBs inhibit effects of angiotensin II on the vasoconstriction and proliferation of vascular smooth muscle cells, reduce sympathetic activation, increase bradykinin dependent vasodilator effects and increase Ang(1-7), a metabolite of angiotensin, which has vascular protective properties. ARBs also interfere with the interactions of the renin-angiotensin-system with both the endothelin-system and the sympathetic nervous system.

Under *in vivo* conditions in men, ARBs have a potent antihypertensive effect and have fewer side effects than any other class of antihypertensives. The available ARBs differ regarding their metabolism, plasma half-life and trough-to-peak-ratio. Several clinical trials have proven that ARBs are safe and effective in reducing morbidity and mortality in hypertension, diabetic and non-diabetic renal disease, acute myocardial infarction as well as systolic and diastolic heart failure. Importantly, protection from cerebrovascular disease and from cardiovascular disease after stroke is an emerging property of ARBs and is likely to be partially independent from the blood-pressure lowering effects. ARBs, similarly to ACE-inhibitors and in contrast to diuretics, have proven to reduce the incidence on new-onset diabetes, which is likely to be clinically relevant in the chronic treatment of hypertension and cardiac disease. Furthermore, ARBs reduce the incidence of atrial fibrillation in hypertensive patients. The reasons for these beneficial effects of ARBs are discussed and include improvement of endothelial function and renal hemodynamics, reduction in central nervous sympathetic tone, interaction with the endothelin-system and potent reduction of left ventricular hypertrophy.

Thus, ARBs are an important new, well tolerated class of cardiovascular drugs, which reduce morbidity and mortality from cardiac, renal and cerebrovascular disease.

1. INTRODUCTION

Blood pressure is regulated by several highly sophisticated systems in the human body, mainly the sympathetic nervous system (SNS), the Renin-Angiotensin system (RAS) and the vascular endothelium (Fig. 1) [1]. Arterial hypertension is one of the most important cardiovascular risk factors in our industrialized world. Various studies including the NHANES population (USA, Canada) and the WHO-Monica-population (Germany, Austria, Switzerland), show that the prevalence of hypertension is between 25-55% [2-10]. Hypertension is an important risk factor for Coronary artery disease (CAD); however, the most important sequelae of hypertension are stroke. Furthermore, hypertension is an important risk factor for atrial fibrillation; more than 70% of patients with atrial fibrillation are hypertensive [11]. One of the broadly underestimated sequelae of hypertension is end stage renal disease; several trials have shown that hypertension leads to end stage renal disease independently from other renal disease states [12, 13]. Furthermore, arterial hypertension can induce congestive heart failure with and without CAD [14].

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Table 1. Snapshot on ARBs

ARBs ...	
•	Are effective and well tolerated antihypertensive drugs
•	Act at the level of the vascular wall, the central nervous system and the kidney
•	Improve endothelial function
•	Reduce left-ventricular hypertrophy
•	Are the drugs of choice for the treatment of diabetic and non-diabetic nephropathy (together with ACE-inhibitors)
•	Reduce the incidence of stroke (possibly more effective than conventional therapy)
•	Reduce the incidence of new-onset diabetes and new-onset atrial fibrillation in hypertensive patients
•	Are similarly effective as ACE-inhibitors to reduce mortality in systolic heart failure
•	Are recommended from several hypertension societies together with diuretics, betablockers, ACE-inhibitors and calcium antagonists as first-line therapy in hypertension (ESH, 2003)

The treatment of elevated blood pressure reduces cardiovascular morbidity and mortality; this has been shown for most of the available antihypertensive drugs. Thus, reducing blood pressure per se independently from the drug class used

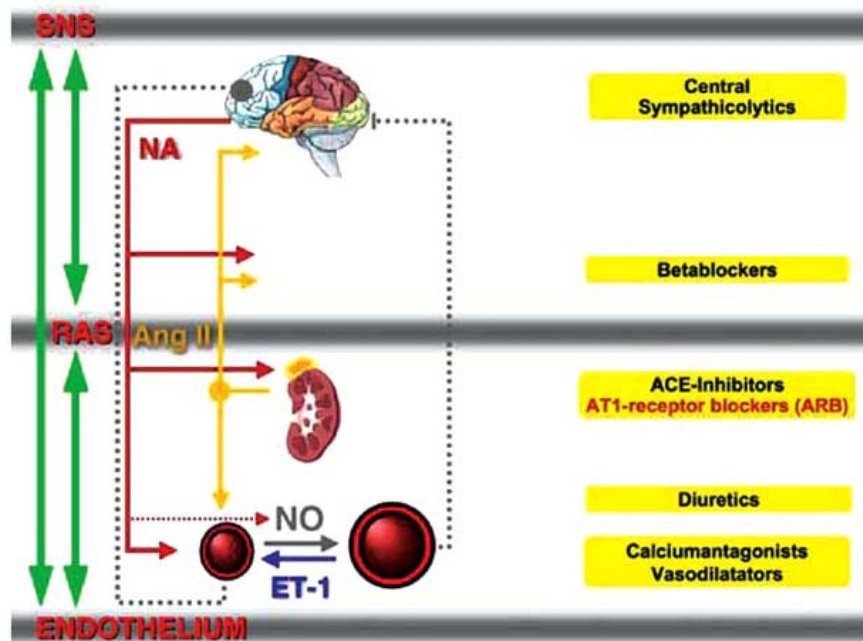


Fig. (1). Antihypertensive drug classes and their point of attack. SNS: sympathetic nervous system; RAS: renin-angiotensin system; NO: nitric oxide, NA: noradrenaline, ET: endothelin; Ang: angiotensin.

and including non-pharmacological efforts is one of the most potent interventions available (Fig. 1). The ALLHAT-study, published in 2002, is one of the most important studies addressing the effects of different antihypertensive drugs on cardiovascular morbidity and mortality; a calcium-antagonist (amlodipine), an ACE-inhibitor (lisinopril), a diuretic (chlorthalidone) and an alpha-blocker (doxazosin) were compared in more than 30.000 hypertensive patients. Besides the fact, that the alpha-blocker had to be omitted because of an increased mortality [15], there were no differences between the remaining three drug groups regarding total mortality [16]. Therefore, it has been concluded that the cheapest therapy, i.e. a diuretic, is equally potent or even better for the long-term treatment of hypertension.

After the publication of the ALLHAT-trial and other hard-endpoint-trials addressing the role of different antihypertensive regimens on cardiovascular mortality, there was an ongoing, partially highly emotional debate about the consequences and limitations of the results. It is difficult for the general practitioner and sometimes even for the hypertensive expert to distinguish between evidence based arguments, industrial marketing and emotion. Should any hypertensive patient be treated with a diuretic as first-line therapy? If so, are the diuretics used in other countries (e.g. hydrochlorothiazide) comparable to chlorthalidone? The debate about new-onset diabetes was introduced. In ALLHAT, there was a significantly higher rate of new-onset diabetes in patients treated with the diuretic compared to the group treated with the ACE-inhibitor [16]. Was the mean follow up of 4.9 years too short to assess the deleterious effects of this important risk factor on cardiovascular morbidity?

In the recent years, several new trials have been published with a new class of drugs, the angiotensin-2-receptor blockers (ARB); there is no doubt that this new

class of drugs has a beneficial effect on cardiovascular morbidity [17]. Nevertheless, they are still more expensive than other established antihypertensive drugs and thus, the cost-effectiveness is under discussion [18]. These trials have added knowledge, but also confusion, to the rational issues for the daily treatment of our patients. Today, we are confronted with a growing number of elderly patients with a growing number of risk factors with sometimes markedly elevated blood pressure levels. It is a matter of fact that most (more than 70%) of the hypertensive patients need combination therapy to reach goal BP levels; this has been shown by many studies including the HOT-study [19].

The present review discusses the role of ARBs in the complex and challenging treatment of hypertension and addresses the issue, under which circumstances there may be an advantage for these new excellent but also expensive class of drugs.

2. HOW DO ARBs WORK?

Angiotensin II is an important mediator in the human body, which is synthesised in several steps (Fig. 2) [1, 20]. Its main action is vasoconstriction, but angiotensin II stimulates proliferation of cells including vascular smooth muscle cells and cardiac myocytes. Thus, an enhanced activity of the RAS leads to a remodeling of blood vessels with increased intimal thickening and ventricular hypertrophy. Importantly, angiotensin II activates the SNS *via* a central nervous mechanism. On the other hand, sympathetic activation leads to renin release through activation of renal beta-1-adrenoceptors [21]. A metabolite from angiotensin II, angiotensin IV inhibits fibrinolysis and promotes the development of free radicals thus deteriorating endothelial function and promoting thrombosis. On the other side, angiotensin(1-7), another metabolite from angiotensin I and

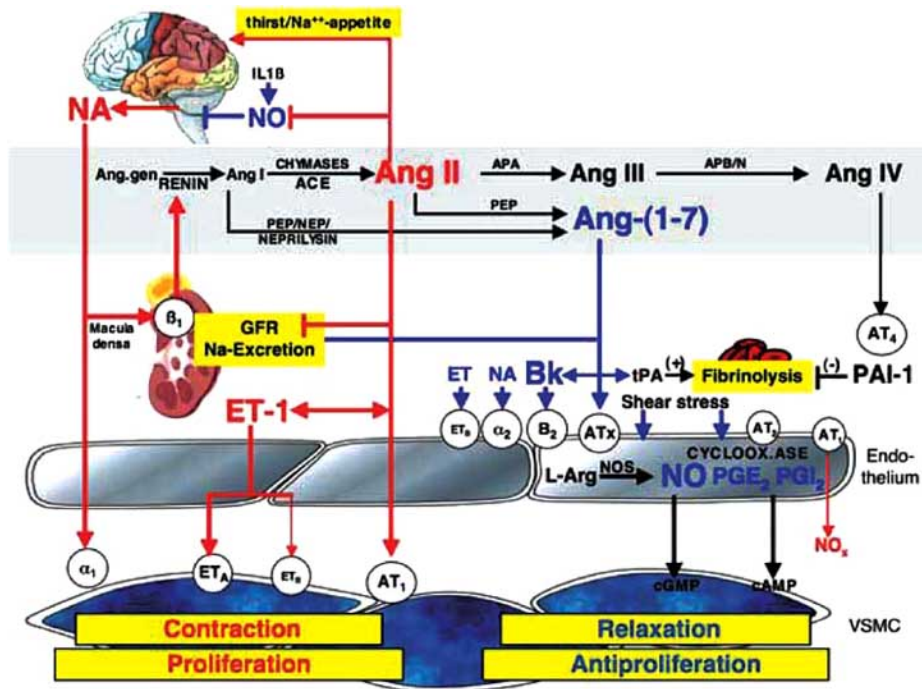


Fig. (2). Scheme of the effects of the renin-angiotensin system on vascular smooth muscle cells (VSMC), vascular endothelium, kidney and central nervous system. NO: nitric oxide. NA: Noradrenaline. AT: angiotensin receptor. Ang: angiotensin. ET: endothelin; BK: Bradykinin.

II, is a vasodilator, an inhibitor of proliferation and increases fibrinolysis [1, 20]. Under physiological conditions, there is a beautiful balance between these intensely interacting endogenous systems; however, under pathophysiological conditions, e.g. an overactivity of the SNS or the RAS and /or endothelial dysfunction, the imbalance leads to an overactivity of the pressor and the proliferating systems. This imbalance seems to be partially genetically determined [22-25].

ARBs inhibit the effects of angiotensin on different levels; they block the effects of angiotensin II on vascular smooth muscle cell contraction and proliferation *via* AT1-receptors without inhibiting the antiproliferative effects of the AT2-receptor. Furthermore, some ARBs may inhibit central sympathetic activity and reduce endothelin-1 plasma levels and thus contribute to BP reduction and other beneficial effects at the level of the endothelium [1]. Both ACE-inhibitors and ARBs enhance ang(1-7) plasma levels leading to an enhanced activity of bradykinin and other mediators which improve NO release and thus endothelial function [20]. Thus, there is a lot of evidence from experimental studies that the selective blockade of the AT1-receptor with ARBs has important beneficial effects beyond BP reduction. Nevertheless, these are surrogate markers and it is important to go into the clinical trials addressing hard endpoints.

There are several ARBs on the market, which differ regarding metabolism and half-life (Table 2). However, it must be emphasized that the plasma half-life may not necessarily reflect the receptor half-life. Furthermore, there may be pharmacologically active metabolites with longer half-lives.

3. ARBs AND STROKE

Several experimental trials have suggested a beneficial effect of ARBs on stroke outcome [26-28]. The first clinical trial showing a marked reduction of the incidence of stroke independently from BP reduction was the LIFE-trial. In this study, more than 9000 hypertensives aged 50-80 years were treated with either the betablocker atenolol (50-100 mg) or the ARB losartan (50-100 mg) for up to 60 months despite a similar BP reduction with both drugs, the incidence of stroke was significantly lower (-25%) in the group of patients treated with losartan. There was a trend towards a lower cardiac mortality and a significantly stronger reduction in left ventricular hypertrophy [29, 30]. Furthermore, the side effect profile of losartan was better when compared to atenolol and there were fewer drop-outs in the ARB group [29].

ARBs have also been studied in patients with acute stroke. The ACCESS trial randomized patients with acute stroke to either placebo or the ARB candesartan (4mg per day) within the first 7 days after the acute stroke; after this period, all patients received the ARB and conventional therapy. The study was stopped previously after 342 pts had been included because of a significantly lower cardiovascular mortality (-50%) in the group of patients treated with the ARB (Fig. 3) [31]. The results of this study are difficult to interpret; why does the treatment with a low dose ARB early after an ischemic stroke lead to a reduction in cardiac mortality? How can a 7-day treatment with an ARB still have an effect several months later?

The MOSES trial looked in a similar design at the effects of the ARB eprosartan after acute stroke [32]. In this study, hypertensive patients with a cerebrovascular event within the

Table 2. List of ARBs Available

	Half-life (h)	CYP450 Interaction	Dose reduction in Hepatic insufficiency	Dose reduction in renal failure
Losartan	2 (-6)*	yes	No	If creatinine clearance < 30 ml/min
Eprosartan	5-9	no	No	If creatinine clearance < 30 ml/min
Valsartan	6	minor	Reduction	If creatinine clearance < 10 ml/min
Candesartan	9	minor	Reduction	If creatinine clearance < 20 ml/min
Irbesartan	11-15	2C9	no	If creatinine clearance < 30 ml/min
Olmesartan	11-15	no	no	If creatinine clearance < 30 ml/min
Telmisartan	24	no	Reduction	If creatinine clearance < 20 ml/min

*Partially active metabolite: 15 hrs.

last 24 months were randomized to receive either a calcium antagonist (nitrendipine) or the ARB eprosartan. BP reduction was similar in both groups; however, the combined endpoint (total mortality, cerebrovascular and cardiovascular event rate) as well as cerebrovascular event rate were significantly lower in the group of patients treated with the ARB [32].

The SCOPE-study assessed the effects of candesartan versus placebo on top of standard antihypertensive therapy in nearly 5000 elderly patients with hypertension. The primary end point showed no significant effect of the drug on cardiovascular events; there was a trend towards a reduction of non-fatal stroke (-30%); however, BP reduction in this trial was stronger with the ARB compared to the placebo group [33].

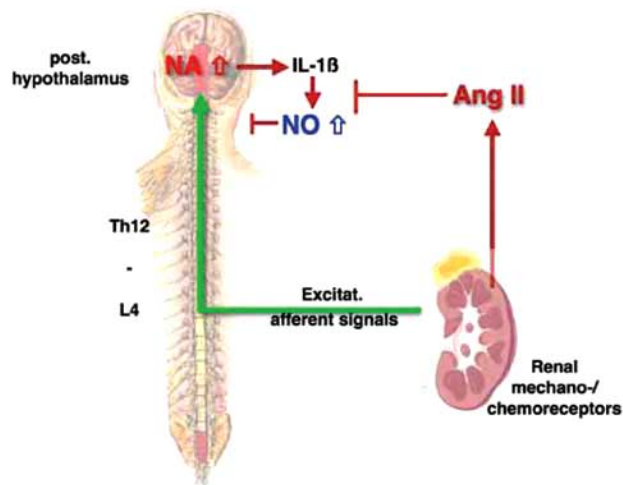


Fig. (3). Scheme of the cerebro-renal efferent and afferent neuronal interaction (details see text). Ang: angiotensin, NA: noradrenaline, IL: Interleukin. NO: nitric oxide.

In summary, the above-mentioned trials hint towards a protective role of ARBs against stroke, which seem to be independent from BP reduction.

4. LEFT VENTRICULAR HYPERTROPHY (LVH) AND SYSTOLIC/DIASTOLIC HEART FAILURE

LVH is an independent risk factor for mortality including sudden cardiac death. In general, any antihypertensive therapy leads to a reduction of LVH and thus to a reduction of sudden cardiac death. However, there seem to be differences regarding the power and rate in the reduction of LVH between antihypertensive drugs. Several experimental and clinical trials have shown that inhibitors of the RAS, i.e. ACE-inhibitors and ARBs, are potent inhibitors of LVH. Many trials have used the ECG criteria for LVH; however, echocardiographic assessment of LVH in experienced hands has a higher specificity to assess LVH and allows measurement of left ventricular muscle mass with a relatively high precision.

The LIFE study assessed the reduction of LVH *via* ECG criteria and found a stronger reduction of LVH in the group of patients treated with losartan [29, 30]. Other ARBs including valsartan have shown similar effects on LVH [34].

A large meta-analysis of 80 trials covering more than 4000 patients assessed the effects of the different antihypertensive drugs (diuretics, betablockers, calcium antagonists, ACE-inhibitor and ARBs). Only studies using echocardiographic criteria for LVH were allowed. The major result was that ACE-inhibitors and ARBs were significantly more potent than diuretics and betablockers in reducing LVH [35].

Diastolic dysfunction is defined as a cardiac dysfunction in which left ventricular filling is abnormal and is accompanied by elevated filling pressures [36]. Among patients who have heart failure, as many as 40 to 60 percent have normal systolic function, which is usually defined as a left

ventricular ejection fraction (LVEF) >50 percent [36]. This condition has been labeled "heart failure with preserved systolic function" [37]. In such patients, diastolic dysfunction is the presumed cause of heart failure, which can be confirmed by objective measures including mitral valve Doppler flow showing an abnormal E/A ratio of left ventricular inflow. However, under clinical circumstances, clinical symptoms of heart failure with preserved LV function allow the diagnosis of isolated diastolic heart failure.

The ACC/AHA guidelines suggest the following therapeutic aims to treat diastolic heart failure: control of systolic and diastolic hypertension, control of ventricular rate in patients with atrial fibrillation, control of pulmonary congestion and peripheral edema with diuretics and coronary revascularization in patients with CAD in whom ischemia is judged to have an adverse effect on diastolic function [36].

Unfortunately, by now, there are only a few studies addressing the role of antihypertensive drugs on diastolic heart failure. The CHARM trial addressed this issue in the "preserved" arm; patients with preserved systolic function (LVEF >40%) but impaired diastolic function and/or clinical symptoms of heart failure were included to receive either placebo or candesartan on top of conventional therapy [38]. The treatment with the ARBs lead to a decrease in hospital admissions due to heart failure without an effect on cardiovascular mortality.

Severe systolic heart failure is the end-point of ischemic heart disease, hypertension and other pathophysiological conditions leading to congestive heart failure (CHF). The treatment of CHF is challenging and aims to reduce the extremely high mortality and improve life quality of these patients. Since many years, ACE-inhibitors, diuretics and betablockers are well established in the treatment of CHF and have proven to reduce total mortality. It is not the aim of this article to review the large evidence of studies in CHF. Several ARBs (losartan, valsartan, candesartan) have shown to be similarly potent when compared to ACE-inhibitors in reducing mortality in CHF patients as well as after acute myocardial infarction; this has been proven in several trials; ELITE II, VALHEFT, and CHARM [39-42]. There is, however, still controversy, whether adding an ARB to the baseline therapy with an ACE-inhibitor and a betablocker has any benefit or might be even harmful for the patient. Indeed, in VALHEFT, the combination therapy with an ACE-inhibitor, a betablocker and an ARB (valsartan) in subgroup analysis showed no further risk reduction or even an increased mortality risk, whereas in CHARM, adding the ARB (candesartan) on top of an ACE-inhibitor and a betablocker regimen was neutral.

The role of ARBs after acute myocardial infarction has been addressed in the VALIANT trial; the ARB valsartan was not superior to the ACE-inhibitor captopril in high-risk patients; the combination of the ARB with captopril even led to an increased rate of hospitalization [42]. Similarly, in the OPTIMAAL study, the ARB losartan was not significantly different to the ACE inhibitor captopril in the reduction of cardiovascular events in high-risk patients with an acute myocardial infarction [43]. The VALUE trial addressed the role of ARB (valsartan) compared to the calcium channel

blocker amlodipine in high-risk hypertensive patients; in this trial, valsartan was not superior to amlodipine in reducing cardiovascular events [44].

Thus, ARBs are well established for the treatment of the dangerous hypertrophy of cardiac myocytes and in overt systolic dysfunction, i.e. congestive heart failure. Furthermore, ARBs improve diastolic function, which is an important mechanism of cardiac function, exercise capacity and – last but not the least – life quality of our hypertensive patients. Nevertheless, there is still controversy about the superiority of ARBs compared to ACE-inhibitors in subgroups of cardiac patients, i.e. after an acute myocardial infarction.

5. NEPHROPROTECTION IN DIABETIC AND NON-DIABETIC NEPHROPATHY

Well before inhibitors of the RAS had been introduced, it has been shown that treatment of hypertension with "conventional" therapy, i.e. betablockers and diuretics, can slow the progression of renal failure in patients with renal disease [45]. Thus, any BP reduction therapy protects the glomerulus against the damage from elevated intraglomerular pressure. In 1993, EJ Lewis published an important trial showing that the ACE-inhibitor captopril slows the deterioration in renal function in patients with diabetic (type 1) nephropathy [46]. Today, ACE inhibitors are well established in the treatment of diabetic and non-diabetic nephropathy; a variety of studies have proven the extensive nephroprotective effects of ACE-inhibitors [47].

ARBs have meanwhile been studied in diabetic and non-diabetic nephropathies; in the RENAAL trial, which included more than 1500 patients with diabetic nephropathy, the ARB losartan reduced the progression of renal failure when compared to placebo on top of conventional antihypertensive therapy [48]. Similar results were achieved in two studies assessing the effects of the ARB irbesartan in patients with type-2-diabetes and microalbuminuria or overt nephropathy [49, 50]. However, in both RENAAL and IDNT, no effect on cardiovascular event rate could be observed in these trials. Whether ARBs are equally potent in terms of nephroprotection as ACE-inhibitors was addressed in another well-designed study in 250 patients with type 2 diabetes comparing the effects of the ARB telmisartan with the ACE-inhibitor enalapril; no differences were observed after 5 years of treatment regarding the deterioration of GFR, cardiovascular events, the rate of end stage renal failure and total mortality [51].

Several trials have assessed the effects of ARBs on the progression of non-diabetic nephropathy. ARBs as well as the combination with an ACE-inhibitor seems to have nephroprotective properties, which go beyond the effects attributable by the reduction in systemic blood pressure; these beneficial effects of combination therapy with an ACE-inhibitor and an ARB have also been shown in patients with diabetic nephropathy [52-61]. Thus, the current recommendations suggest combination therapy (ACE-inhibitor and ARB) in high-risk renal patients with proteinuria >1g/day despite optimal blood pressure control with RAS inhibitors [47].

6. NEW-ONSET DIABETES

New onset diabetes is an additional risk factor in hypertensive patients; most of the patients develop cardiovascular

disease years or even decades after the onset of diabetes. There seem to be differences in the risk to develop new-onset diabetes between antihypertensive drug classes. Under a diuretic therapy, the risk to develop diabetes is significantly higher than with ACE-inhibitors. This has been documented as secondary endpoint in different trials assessing the effects of calcium-channel blockers, betablockers and diuretics [19, 62, 63]. One of the largest trials in hypertension, the ALLHAT trial documented a significantly higher rate of new-onset diabetes with the diuretic chlorthalidone (11.6%) when compared to the ACE inhibitor lisinopril (8.1%) and the calcium antagonist amlodipine (9.8%) [16].

Interestingly, several trials with ARBs in hypertensives and heart failure patients have shown similar results, i.e. a reduction in the rate of new-onset diabetes after treatment with an ARB. In the LIFE-study, the rate of new-onset diabetes was significantly lower with losartan compared to atenolol [29]. The CHARM study, which assessed the effect of candesartan on cardiovascular mortality in congestive heart failure patients, the rate of new onset diabetes was again significantly lower with the ARB compared to placebo [40].

It is unclear whether these beneficial effects of ARBs and ACE-inhibitors on the development of diabetes result in a reduction of cardiovascular morbidity and mortality. However, it is unlikely that these effects could be assessed in a trial of 3-5 years mean duration time as in the ALLHAT trial. Thus, prospective, long-term studies would be needed to address this issue.

7. NEW-ONSET ATRIAL FIBRILLATION

Atrial fibrillation is a growing risk factor for stroke in hypertensive patients. Angiotensin II contributes to the development of atrial fibrillation by shortening the effective refractory period of the atria during tachycardia [64]. There is evidence from experimental trials that the blockade of the RAS reduces the probability to develop atrial fibrillation [64, 65]. Genetic variations, including polymorphisms of the RAS, may be associated with non-familial atrial fibrillation [66]. In clinical trials, ARBs have shown to reduce the risk of new onset atrial fibrillation; this has been documented for losartan (subanalysis of the LIFE study) and valsartan (subanalysis of the Val-HEFT) [67, 68]. The relevance of these findings is high, as a reduction of the incidence of atrial fibrillation is likely to contribute to the direct risk of stroke and may explain the blood pressure independent reduction of stroke seen with ARBs in the mentioned clinical trials. Furthermore, indirectly threatening side effects of anticoagulation necessary in patients with atrial fibrillation can be overcome.

8. POSSIBLE EXPLANATION OF THE BENEFICIAL EFFECTS OF ARBS

Several experimental data show a variety of effects at the level of the CNS and the vascular endothelium as well as the fibrinolysis, which may in part explain the beneficial effects seen in clinical trials. For certain ARBs (i.e. losartan, candesartan, valsartan) an improvement of endothelial function, a reduction of oxidized LDL and an increase of fibrinolysis have been documented [69-74]. Inhibitors of the

RAS (ACE-inhibitors, ARBs) have sympatholytic effects [75]. This has been shown under clinical conditions (metabolic syndrome, heart failure) for valsartan, losartan and candesartan [76-78]. Another important effect of ARBs is related to the reno-cerebral interaction; inhibition of angiotensin II reduced the efferent sympathetic stimulatory effects on the renal circulation as well as the centripetal excitatory effects of the kidney; this leads to a reduction in sympathetic tone and thus, to a reduction in blood pressure (Fig. 3) [79, 80]. The antidiabetic effects of inhibitors of the RAS are supposed to be related to their stimulatory effects on the PPAR gamma receptor, which enhances insulin sensitivity (for details see cited reviews) [81-83]. The RAS importantly interferes with the endothelin-system; endothelin-antagonists inhibit the vasoconstrictive and proliferative effects of angiotensin II [25, 84, 85]. On the other hand, blockade of the AT1 receptor interferes with the effects and possibly the release of endothelin [70, 86]. Thus, ARBs, *via* inhibition of the endothelin system, may have a beneficial role on cardiac myocytes, cardiac conductivity, vascular smooth muscle cells and on endothelin-1 mediated neuronal mechanisms.

Whether these experimental and clinical surrogate markers explain the beneficial effects of RAS-inhibitors on hard endpoints remains unclear. Nevertheless, sympathetic activity and endothelial function correlate with cardiovascular morbidity and mortality. Thus, any drug, which affects these systems, is likely to have beneficial effects on clinical endpoint beyond the sole blood pressure reduction.

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