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REVIEW

Angiotensin receptor blockers: Therapeutic targets and cardiovascular protection

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Abstract

In the prevention and treatment of cardiovascular disease, pharmacological treatment strategies should have several aims: (i) in individuals without overt cardiovascular disease, but with risk factors such as hypertension and/or diabetes, pharmacotherapy should prevent or delay disease development; (ii) in patients who have already progressed to cardiovascular disease, pharmacotherapy should help either to prevent or regress target organ damage (TOD); and (iii) in patients with TOD, pharmacotherapy should prevent events. Any medication intended for long-term therapy also should be well tolerated. Inhibiting the renin–angiotensin system has proven a successful therapeutic strategy in cardiovascular and renal medicine. Angiotensin-converting enzyme (ACE) inhibitors have demonstrated important advantages over conventional agents such as beta-blockers and thiazide diuretics, and have become a relevant part of treatment for heart failure post-myocardial infarction, left ventricular dysfunction and renal disease. Tolerability concerns may prevent their use in some patients, however. Angiotensin AT1 receptor blockers (ARBs) provide a different form of blockade of the renin–angiotensin system and a growing body of evidence suggests that this alternative approach may confer additional cardiovascular protection for some patient subgroups. In addition, ARBs generally are better tolerated than ACE inhibitors, enhancing patient compliance and persistence with long-term therapy. Furthermore, evidence in favour of combining an ACE inhibitor and an ARB in certain circumstances is continuously growing.

Key Words: *Angiotensin AT1 receptor antagonists, cardiovascular diseases, hypertension, renin–angiotensin system*

Introduction

Essential hypertension is one of the most important contributors to cardiovascular diseases, the leading cause of premature death and associated with considerable morbidity worldwide (1). Recently three relevant contributions have come to extend the knowledge of the relevance of elevated blood pressure. The first was the Comparative Risk Assessment project (2), which demonstrated that examining 20 different causes of global burden of disease, high blood pressure was the leading cause of death either in developed and underdeveloped

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countries. The second (3) showed that the relation between blood pressure and cardiovascular risk is a continuous one from values of 115/75 mmHg and the risk doubles for each increase of 20 mmHg in systolic and/or 10 mmHg in diastolic. The third (4) predicts that in the near future more than 1.5 billion hypertensives will require medical attention in our world. Hence, efforts to improve lifestyle in order to reduce cardiovascular risk factors should form part of any preventive cardiovascular health programme.

However, a large proportion of hypertensive patients will also need drug therapy to lower blood pressure. Modern (albeit arbitrary) definitions of hypertension indicate that over one-third of adults over 16 years of age, more than half of those aged over 55 years and about three-quarters of those over the age of 65 years are hypertensive. A large proportion of the adult population therefore requires medication to lower blood pressure, according to current guidelines (5–7).

Antihypertensive medications have evolved over the last half-century, with enormous strides made towards many of these ideal requirements. Inhibiting the renin–angiotensin system has proven a successful therapeutic strategy. Angiotensin-converting enzyme (ACE) inhibitors are effective drugs and have been shown to be particularly beneficial in a number of cardiovascular disorders (8,9). However, many patients require additional therapy to reach current blood pressure targets. On the other hand, ACE inhibitors are not always well tolerated. Consequently, there has been increasing interest in alternative and complementary methods for inhibiting the renin–angiotensin system in patients with cardiovascular disease, particularly angiotensin AT1 receptor blockers (ARBs). A growing body of evidence now indicates that ARBs are well-tolerated and effective antihypertensive agents, which provide cardiovascular protection (8,9).

The favourable profile of the ARBs in hypertension and their specific and distinctive differences compared with ACE inhibitors prompted an early inclusion of ARBs among the first-choice drugs recommended in the 1999 international guidelines for the treatment of hypertension (10). This recommendation has been reiterated and reinforced in all sets of international guidelines published in 2003 (5–7,11). These guidelines also emphasize the evidence-based indications for ARBs in specific subgroups of hypertensive patients with comorbid illnesses.

This paper reviews ARBs evaluating whether or not they meet the requirements of an ideal antihypertensive medication and whether they possess additional advantages over their antihypertensive effects to prevent or delay the vascular consequences of elevated blood pressure.

Mechanisms of action and potential therapeutic role

Angiotensin II-mediated vasoconstriction, and renal salt and water retention contribute to arterial hypertension and compromise the pumping ability of the failing heart. AT1 receptor-mediated growth-promoting effects participate in vascular and left ventricular hypertrophy, diabetic nephrosclerosis, neointima formation and atherothrombosis, as well as in structural remodelling of the heart following myocardial infarction.

Angiotensin II, acting via the AT1 receptor, also may be instrumental in loss of brain function after brain ischaemia (12), and appears to participate in inflammatory responses and in the production of free oxygen radicals with adverse effects on endothelial function and post-ischaemic repair (Figure 1) (13).

Several of the AT2 receptor-mediated actions of angiotensin II, on the other hand, seem to antagonize those of the AT1 receptor. In the adult organism, the AT2 receptor is frequently suppressed. Tissue injury dramatically up-regulates its expression, however, helping to restore endothelial function, for instance by producing nitric oxide (14), and preventing vascular and cardiac cell growth.

Since the advent of the ACE inhibitors, and of the ARBs, many experimental and clinical have demonstrated that inhibition of the renin–angiotensin system at different levels can attenuate several pathophysiological actions of angiotensin II mediated by the AT1 receptor and thus protect vital organs to reduce cardiovascular morbidity and mortality (8).

In contrast to the ACE inhibitors, however, the ARBs do not reduce angiotensin II concentrations. Instead, the ARBs produce a selective, dose-dependent blockade of the AT1 receptor, independently of the different pathways of angiotensin II generation (13). Thus, the ARBs prevent the chymase-mediated angiotensin II production that can occur in the presence of ACE inhibitors. The chymase pathway is known to contribute to the ''escape'' phenomenon, in which both angiotensin and aldosterone levels, initially lowered by ACE inhibition, eventually increase to pre-treatment levels (15–17). In addition, in the presence of AT1 receptor blockade, the binding of angiotensin II to the unopposed AT2 receptor may provide additional

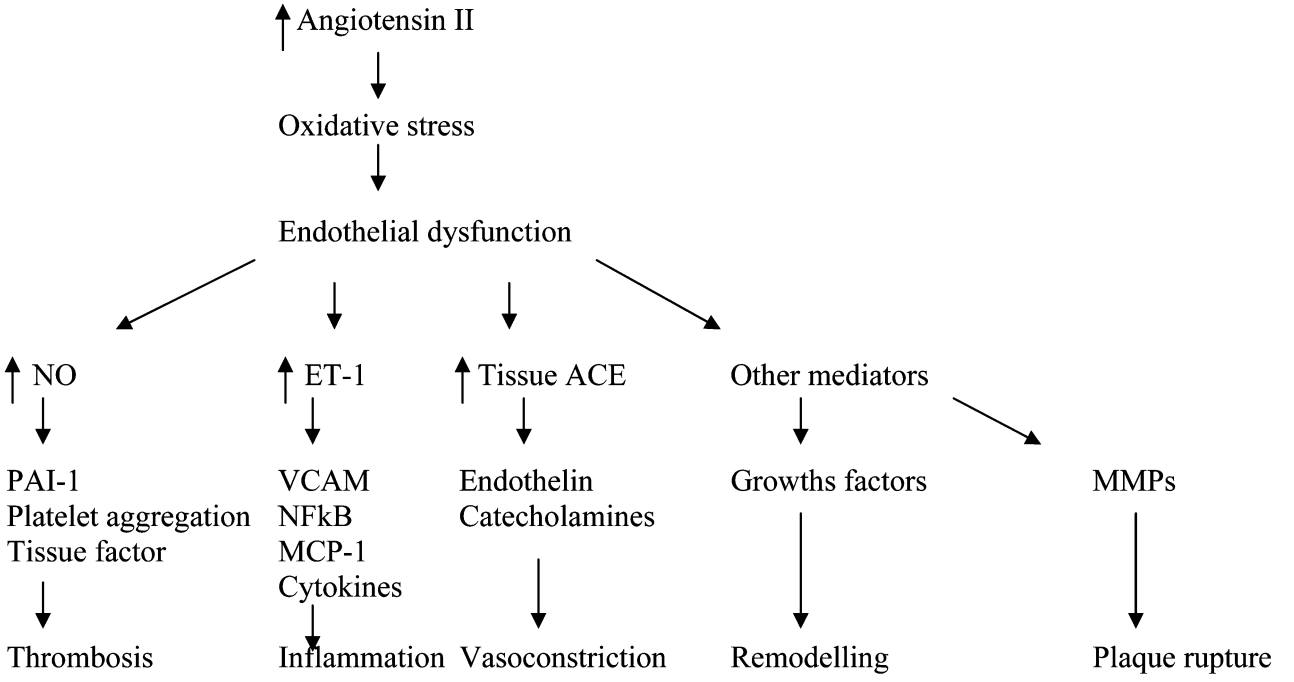

Figure 1. Schematic representation of the multiple effects of increased tissue production of angiotensin II. ET-1, endothelin-1; MCP-1, monocyte chemoattractant protein–1; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NO, nitric oxide; PAI-1, plasminogen activator type 1; VCAM, vascular cell adhesion molecule.

beneficial effects (18). Indeed, stimulation of AT2 receptors following AT1 blockade has already been shown in animal experiments to be involved in tissue repair following myocardial infarction or injury of the nervous system (19–21).

Preclinical and short-term clinical studies have demonstrated that ARB are effective in lowering BP and offer additional cardiac, cerebral and renal protection (Table I) (22).

Effects of ARBs on BP and ambulatory BP

The extent of blood pressure reduction with ARBs is comparable to that achieved with all other first-choice classes of antihypertensive drugs (23). This effect is dose dependent (24).

All ARBs have been shown to reduce 24-h average blood pressure in hypertensive patients when administrated as monotherapy and their efficacy is greater when combined with a low dose of diuretic or any member of the other classes of antihypertensive drugs (25).

Tolerability, compliance and persistence

Studies performed in many countries around the world consistently show that adequate blood pressure control is achieved and maintained in only a small minority of the hypertensive population (5,6). This has negative public health consequences because cardiovascular risk is substantially greater for individuals with a blood pressure of at least 140/90 mmHg compared with those with lower blood pressure levels (26).

The reasons for this poor control of hypertension worldwide continue to be the focus of considerable interest and effort. One reason may be that physicians still often base antihypertensive treatment on monotherapy (27). A recent meta-analysis of 119 randomized, double-blind, placebo-controlled trials with thiazides, beta-blockers, ARBs and calcium-channel blockers has confirmed that combination therapy improves antihypertensive efficacy and tolerability (28). The first and second drugs, when given separately, lowered blood pressure by an average of 7.0/4.1 and 8.1/4.6 mmHg, respectively, compared with 14.6/8.6 mmHg when the two drugs were combined. In some trials, a major blood pressure reduction (13.3/7.3 mmHg) was achieved when the antihypertensive agents were administered at half-standard doses.

Achieving the blood pressure targets needed to protect patients effectively is particularly difficult even in trials where expert physicians are treating more highly motivated patients, are using in most

Table I. Clinical evidence for the angiotensin II receptor blockers (ARB).

Trial	Patient population	Median follow-up	Treatment arms	Effects
LIFE	Essential hypertension	4.8 years	Losartan vs atenolol	↓ BP similar in both arms ARB ↓ incidence of combined endpoint (death, MI, or stroke) rr=0.87, 95% CI 0.77–0.98, p=0.021
SCOPE	Elderly with elevated BP	3.7 years	Candesartan vs diuretic or β-blocker	Greater ↓ BP with candesartan No difference between treatments for combined endpoint of CV death, non-fatal stroke, and non-fatal MI ARB ↓ incidence of non-fatal stroke by 27.8% (95% CI 1.3–47.2, p=0.04)
VALUE	Essential hypertension, at high CV risk	4.3 years	Valsartan vs amlodipine	Treatment BP with amlodipine by 2.0/1.6 mm Hg lower than with valsartan. Similar primary cardiac endpoint, although cause specific outcome were different (difficult to interpret due to BP differences)
ELITE-II	HF	1.6 years	Losartan vs captopril	All-cause mortality similar in both arms
Val-HeFT	HF	23 months	Valsartan vs conventional therapy	Overall mortality similar in both arms ARB ↓ incidence of combined endpoint (mortality and morbidity) by 13.2% (rr=0.87, 97.5% CI 0.77–0.97, p=0.009)
CHARM	CHF	3.1 years	Candesartan vs conventional therapy	ARB ↓ incidence of combined endpoint of CV death and hospital admission for CHF (hazard ratio 0.84, 95% CI 0.77–0.91, $p<0.0001$)
OPTIMAAL	MI and HF	4 years[a]	Losartan vs captopril	All-cause mortality similar in both arms
VALIANT	MI and HF	2 years	Valsartan vs captopril vs valsartan plus captopril	ARB as effective as ACE inhibitor and ARB+ACE inhibitor in reducing all-cause mortality (primary endpoint: 19.9%, 19.5%, and 19.3%, respectively). ARB ↓ side-effects compared with ACE inhibitor or ARB+ACE inhibitor combination
RENAAL	Type 2 diabetes and nephropathy	3.4 years	Losartan vs conventional therapy	ARB ↓ incidence of combined endpoint (doubling of baseline Cr, ESRD, death) by 16% (p=0.02)
IDNT	Type 2 diabetes and nephropathy	2.6 years	Irbesartan vs amlodipine vs placebo	ARB ↓ incidence of combined endpoint (doubling of baseline Cr, ESRD, death) by 20% (p=0.02) compared with placebo and by 23% (p=0.006) compared with amlodipine
IRMA-2	Type 2 diabetes and microalbuminuria	2 years	Irbesartan vs placebo	ARB ↓ incidence of primary endpoint (time to onset of diabetic nephropathy) from 14.9% on placebo to 5.2% on irbesartan (hazard ratio 0.3, 95% CI 0.14–0.61, $p<0.001$)
MARVAL	Type 2 diabetes and microalbuminuria	24 weeks	Valsartan vs amlodipine	ARB ↓ UAER from baseline compared to amlodipine (56% vs 92%, $p<0.001$)

ACE, angiotensin-converting enzyme; BP, blood pressure; CHF, congestive heart failure; CI, confidence interval; Cr, serum creatinine concentration; CV, cardiovascular; ESRD, end-stage renal disease; HF, heart failure; MI, myocardial infarction; rr, relative risk; UAER, urinary albumin excretion rate. Trial abbreviations: CHARM, Candesartan in Heart Failure to Affect Reduction in Morbidity and Mortality; ELITE, Evaluation of Losartan in the Elderly; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA-2, IRbesartan type 2 diabetes with MicroAlbuminuria; LIFE, Losartan Intervention For Endpoint reduction trial; MARVAL, MicroAlbuminuria Reduction with VALsartan; OPTIMAAL, Optimal Trial In Myocardial infarction with the Angiotensin II Antagonist Losartan; RENAAL, Reduction in End Points in NIDDM with the Angiotensin II Antagonist Losartan; SCOPE, Study on COgnition and Prognosis in the Elderly; Val-HeFT, Valsartan Heart Failure Trial; VALIANT, VALsartan in Acute myocardial INfarction Trial; VALUE, Antihypertensive Long-term Use Evaluation study. [a]Duration of trial based on achieving the target of 937 deaths. Adapted from (22).

cases combination therapy and follow their patients more closely than would be the case in clinical practice (29). In the general hypertensive population, patients' adherence to the prescribed treatment regimen becomes a key determinant of the success of blood pressure control (30).

Several factors play a role in compliance with the lifestyle changes and antihypertensive drug(s) that may be needed to control hypertension effectively. These include a high acquisition cost, treatment regimen complexity, the information given to the patient about the nature of the disease and the benefit of treatment, and the difficulty and the time involved in consulting the physician and obtaining the prescription.

However, several studies have identified side-effects as the most frequent reason for stopping medication (31). Many patients with asymptomatic conditions, such as hypertension, are unwilling to accept treatment-related problems. The use of drugs without, or with few, side-effects is clearly crucial to the success of antihypertensive treatment in clinical practice. Progress in the field therefore has been marked by the introduction of agents with better tolerability profiles than their predecessors, rather than a superior antihypertensive effect.

The efficacy of ARBs to lower blood pressure either alone or in combination with other drugs is, as previously stated, similar to that of other classes of antihypertensive agents. Their tolerability, however, is superior. A large database shows that, for each member of this class, the incidence of most side-effects is not significantly different from placebo (32,33). Furthermore, there is evidence that ARBs do not impair quality of life and indeed may even improve it, regardless of the therapeutic dose (34). Finally, patients are more likely to persist with long-term treatment when an ARB is prescribed as the initial agent (35).

Strategies intended to reduce the cardiovascular morbidity and mortality of hypertension must not only produce greater reductions in blood pressure but must also treat concomitant risk factors and/or use drugs that directly protect against end-organ damage. Such strategies, if they are to be successful, also must be applicable to a greater proportion of the hypertensive population. Agents with optimal tolerability, such as ARBs, will be needed to achieve this goal.

Combination of an ACE inhibitor and an ARB

Available evidences recently reviewed show that the combination of an ACE inhibitor and an ARB can be contemplated in clinical practice (36–38). Symptomatic heart failure patients with left ventricular systolic dysfunction and patients with chronic renal failure and proteinuria above 1 g/day are two examples of this possibility.

Cardiac outcomes in antihypertensive treatment trials

A recent large meta-analysis of the impact of ACE inhibitors on clinical outcomes in hypertension (39) has shown that, despite their efficacy in lowering blood pressure, ACE inhibitors do not produce cardiovascular outcomes that are significantly superior to those of conventional therapy of hypertension with diuretics and beta-blockers.

A recent meta-analysis in hypertensive patients demonstrated that ARBs significantly reduced, by about 12%, compared with conventional antihypertensive therapy, the relative risk of composite primary cardiovascular endpoints, including stroke, non-fatal myocardial infarction and cardiovascular death (40). The degree of lowering of blood pressure and especially early control of blood pressure seems to be very important, particularly in high-risk hypertensive patients, for the cardiovascular outcome as shown by the data of the Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE) that compared a combination of an ARB/diuretic arm versus a calcium-channel blocker/diuretic arm (41).

Cerebrovascular outcomes in antihypertensive treatment trials

A recent meta-analysis of studies using ARBs (42), including IDNT (43), RENAAL (44), LIFE (45) and SCOPE (46), reveals a reduction in stroke risk with ARB-based, compared with control, regimens. This positive effect is largely due to the findings of the LIFE trial (45). LIFE demonstrated that, in hypertensive patients with left ventricular hypertrophy, losartan reduced the relative risk of stroke, despite a blood-pressure-lowering effect similar to that observed with atenolol. In the SCOPE (Study on Cognition and Prognosis in the Elderly) trial (46), candesartan reduced the relative risk of non-fatal stroke. Data from the VALUE trial (25) showed that the rate of stroke was lower in the amlodipine arm, although not significantly with an increased risk of 15% for the ARB group. However, the differences in blood pressure control between the two groups (significantly lower in the amlodipine arm) have

important implications for the observed results, as the hypothesis of the trial required that similar levels of blood pressure control be achieved.

The efficacy of ACE inhibitors in preventing cerebrovascular disease is similar to that of therapy based either on diuretics and beta-blockers or on calcium antagonists (39,42). The underlying mechanism for this cerebrovascular protection is therefore probably related to blood pressure reduction and ACE inhibitors are unlikely to offer added benefits.

Nevertheless, there is a belief that ACE inhibitors possess a unique ability to prevent stroke that is at least partly independent of blood pressure reduction. Such an interpretation emerged mainly from the results of the HOPE (Heart Outcomes Prevention Evaluation) (47) and PROGRESS (perindopril PROtection aGainst REcurrent Stroke Study) (48) trials. Yet these studies provide, at best, only weak support for this hypothesis. In the HOPE trial, ramipril was associated with a 32% reduction in the relative risk of stroke as compared with placebo. This reduction was associated with a small decease in blood pressure (3.3 mmHg systolic and 1.4 mmHg diastolic), which, at most, could explain only a 13% reduction in stroke. However, in a subgroup of 20 patients undergoing 24-h ambulatory blood pressure monitoring, most of the antihypertensive effect due to ramipril was exerted during the night. This may indicate that daytime office blood pressure measurements may have underestimated the antihypertensive effect of ramipril administered at night-time (49). In the PROGRESS trial, perindopril, which reduced blood pressure by only modestly 5/3 mmHg, did not prevent recurrent stroke. A greater reduction in blood pressure values (by 12/5 mmHg) and in the risk of recurrent stroke was observed only in the group of patients treated with the combination of perindopril and indapamide. It is therefore highly likely that the prevention of cerebrovascular disease associated with ACE inhibition is related to blood pressure reduction *per se* and not to another, specific but not antihypertensive, drug-related effect.

Renal outcomes in antihypertensive treatment trials

Diabetic renal disease

Diabetic nephropathy, a common complication in patients with type 2 diabetes, is the leading cause of end-stage renal disease (ESRD) in the western world (50). In diabetic patients with nephropathy, two large-scale randomized placebo-controlled trials have demonstrated superiority of ARBs over either dihydropyridine calcium antagonists or conventional therapy on renal protection in diabetic patients (43,44).

ACE inhibitors have been considered agents of choice to protect patients with type 1 diabetes against kidney disease progression (5,6). The increasing use of ACE inhibitors to treat the early stage of nephropathy (i.e. microalbuminuria) is a response to the growing emphasis on starting treatment early in the belief that this will prevent future organ damage (5). Here again, the evidences available on the prevention of development of overt diabetic nephropathy in type 2 diabetic patients correspond to data obtained with an ARB in the IRMA-2 study (51) and extended with the demonstration at equal BP control that an ARB valsartan differs from a calcium antagonist by its capacity to lower albuminuria in either normo and hypertensive microalbuminuric type 2 diabetic patients (52).

Recently published data have, however enhanced the capacity of ACE inhibitor in the protection of the kidney in type 2 diabetic patients with the demonstration of the capacity of trandolapril alone or in combination with verapamil for the primary prevention of development of microalbuminuria in hypertensive normoalbuminuric type 2 diabetic patients in the BENEDICT study (53) and also by the data from the DETAIL study (54) showing a similar capacity of enalapril and telmisartan for long-term protection (5 years) of glomerular filtration rate in microalbuminuric type 2 hypertensive diabetic patients. However, no trial with an ACE inhibitor has yet shown positive effects on ESRD or death as single or combined end-points, or on doubling of serum creatinine coupled with ESRD or death (55).

Non-diabetic renal disease

In patients with non-diabetic renal disease, a recent meta-analysis of 11 studies (56) concluded that ACE inhibitors slow the progression of renal disease via a mechanism that is, in part, independent of their blood pressure lowering effects. Recent data from the AASK trial found no further reduction in the progress of renal dysfunction in African-American hypertensives with nephrosclerosis by reducing blood pressure to 128/78 mmHg rather than 141/85 mmHg, but ACE inhibitors were shown to be somewhat more effective than beta-blockers or calcium antagonists (57). ARBs were shown to have similar efficacy to ACE inhibitors in reducing proteinuria and slowing renal disease progression in the COOPERATE study, although their combined

use was superior to monotherapy with either agent (58).

In conclusion, long-term data on the use of ACE inhibitors for renal protection in type 2 diabetes is limited and conflicting. Although ACE inhibitors have shown positive effects against markers of renal disease in patients with type 2 diabetes, there is insufficient clinical evidence to adequately compare these agents with those of other classes of antihypertensive agents in their effects on time to ESRD. In contrast, ARBs have been shown in type 2 diabetes to be superior to other classes of antihypertensive agent in delaying renal disease progression, and to have better tolerability, although no head-to-head comparison with an ACE inhibitor exists. In non-diabetic disease, the COOPERATE trial shows that ARBs and ACE have similar effects in delaying renal progression.

Effects on heart disease progression

Congestive heart failure

In the developed world, congestive heart failure is the cardiovascular disorder with the greatest impact on public health resources (59). Optimal therapy, which can slow the progression of this disease, is based on potent inhibitors of the renin–angiotensin–aldosterone system, which is now know to be central to the pathophysiology of congestive heart failure. Effective inhibition of this system requires a combination of agents to block each of its three main components: a beta-blocker; an aldosterone antagonist; and an ACE inhibitor and/or an ARB to block angiotensin II-mediated effects.

An ARB combined with an ACE inhibitor. Ex vivo studies of human cardiac tissue (60) have shown that complete inhibition of the effects of angiotensin II requires both ACE inhibition and AT1 receptor blockade. Similar conclusions emerged from the RESOLVD (randomized evaluation of strategies for left ventricular dysfunction) pilot trial (61). In the Valsartan Heart Failure Trial (Val-HeFT) (62) a further reduction in cardiovascular morbidity and mortality was achieved with the addition of valsartan, at a daily dose of up to 320 mg, to conventional therapy including an ACE inhibitor. The most marked effect was that of a 27.5% reduction ($p < 0.001$) in hospitalization for heart failure, the most frequent, disabling and costly morbid event associated with the condition. Similar findings were obtained with the addition of candesartan to conventional therapy in the CHARM-added trial (63). In this study, 2548 patients received candesartan in addition to standard therapy, including an ACE inhibitor. These results showed a significant 15% reduction in the primary endpoint of combined cardiovascular mortality and heart failure admission. Candesartan also reduced the total number of hospitalizations for heart failure.

These added benefits may be attributable to the greater sustained reductions in blood pressure and in suppression of plasma noradrenalin (64) and aldosterone (65) achieved with an ARB. Heart failure management guidelines therefore need an update to include the possibility of addition of ARBs to conventional treatment in symptomatic patients.

An ARB instead of an ACE inhibitor. In the Val-HeFT trial, a subgroup analysis, in the heart failure patients intolerant of ACE inhibitors, demonstrated for the first time that the use of valsartan substantially reduced the risk of the combined morbidity and mortality endpoints, including survival and hospitalization for cardiovascular events (66). These results were fully confirmed by the CHARM-alternative trial (67). Both ARBs valsartan and candesartan have the specific indication for heart failure patients.

Various trials have compared the efficacy of ARBs with ACE inhibitors in patients with congestive heart failure. ELITE II (68) and OPTIMAAL (69) both failed to demonstrate non-inferiority for losartan 50 mg once a day compared with captopril, but this may have been attributable to an insufficiently effective dose of losartan.

Post-myocardial infarction (MI)

The RAS is activated in patients with acute MI, as it is in subjects with LV dysfunction and heart failure. Plasma renin activity is also predictive of cardiovascular mortality post-MI. ACE inhibitors reduce mortality, slow progression to heart failure and are of great benefits in high-risk patients (70). Trials of non-selected acute myocardial infarction (AMI) patients, including the Fourth International Study of Infarct Survival (ISIS-4) (ISIS-4 (Fourth International Study of Infarct Survival) (71) and the Third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI-3) (72), showed a modest benefit with ACE inhibitor treatment, with mortality reduced by 7% to 12%. Greater benefits were seen in several trials that focused on selected patient populations (73).

Two studies evaluated the effects of ARBs in post-MI patients. In the VALIANT trial, valsartan 160 mg bid was, in the 14 703 patients with AMI

complicated by heart failure, left ventricular dysfunction or both, at least as effective in reducing the risk of death and cardiovascular death, non-fatal myocardial infarction, or heart failure as a proven dose of captopril (74). The VALIANT findings therefore suggest that valsartan is a clinically effective alternative to an ACE inhibitor. However, in the OPTIMAAL trial (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan), Kenneth Dickstein and colleagues compared losartan and captopril and found a non-significant difference in total mortality in favour of captopril in high-risk patients after AMI. This difference seems mainly driven by a significant excess of cardiovascular deaths in the losartan group (69).

Taken together, the results of trials with ARBs indicate as suggested in recently published reviews (36,37) that these drugs may be used as an alternative to ACE inhibitor therapy in patients following myocardial infarction and in those with heart failure who cannot tolerate ACE inhibitors. They may also be added to ACE inhibitors and other conventional treatments in symptomatic heart failure patients.

Effect on target organ damage and metabolic disorders

Protection against left ventricular hypertrophy

In hypertensive patients, left ventricular hypertrophy (LVH) represents a mechanism of adaptation to abnormal loading. However, LVH is also the first step toward the development of clinical cardiovascular diseases, such as congestive heart failure, ischaemic heart disease, stroke and sudden death (75,76). Several mechanisms have been proposed to explain these increased cardiovascular risks. These include cardiac diastolic and systolic dysfunction, predisposition to arrhythmias, alteration of autonomic nervous system activity, and reduced coronary flow reserve.

Blood pressure reduction by pharmacological treatment may reverse LVH. Increasing evidence demonstrates that changes in left ventricular mass during antihypertensive treatment may directly influence the risk of clinical cardiovascular complications (77). However, different classes of antihypertensive drugs may not be similarly effective in reducing left ventricular mass for the same antihypertensive effect. Certain drugs may interfere differently with several non-haemodynamic factors, which may contribute to the increase in left ventricular mass. These include the renin–angiotensin system, the sympathetic nervous system and growth factors.

Treatment with agents that interfere with the renin–angiotensin system has produced positive effects on cardiovascular structural changes. A meta-analysis of studies of LVH regression has indicated that ACE inhibitors and ARBs, together with calcium-channel blockers, may be more effective than beta-blockers and diuretics in reducing left ventricular mass, for similar blood pressure reductions (78). In LIFE, losartan was more effective than atenolol in inducing LVH regression and provided superior cardiovascular protection (45). In another study in hypertensive patients, valsartan was superior to enalapril in improving diastolic function (79).

In hypertensive patients with cardiovascular hypertrophy, blood pressure reduction by pharmacological treatment may improve and even completely reverse structural changes. Blockade of the renin–angiotensin system may confer an additional benefit beyond blood pressure reduction. To date, as stated in a recent review (80), plenty of echocardiographic studies reported a superiority or non-inferiority of an ARB vs a comparator regimen, including ACE inhibitors in reducing the extent, and consequences, of cardiovascular remodelling.

Protection against arterial vascular hypertrophy

Structural and functional abnormalities of small and large arteries are also frequently observed in patients with arterial hypertension. In small resistance arteries, increased arterial wall thickness and lumen reduction seem to play an important role in the increase of vascular resistance, and may reduce maximal flow reserve, thus inducing a greater change in resistance for any given degree of smooth muscle shortening. In the large elastic arteries of hypertensive patients, an increased stiffness has been described, leading to higher systolic pressure and to an increased load on the heart.

Long-term antihypertensive treatment with ACE inhibitors, calcium antagonists and ARBs also can normalize small resistance artery structure, an effect not achieved with beta-blockers, despite similar blood pressure reductions (81). Renin–angiotensin system blockade was also highly beneficial in Val-PREST (Valsartan for Prevention of Restenosis after Stenting of type B2/C lesions), in which valsartan treatment halved the incidence of restenosis in patients undergoing coronary stenting (82).

Protection against endothelial dysfunction and atherosclerosis

Endothelial dysfunction: possible mechanisms. Angiotensin II exerts a negative effect, via AT1 receptor, on endothelial function by releasing endothelin-1 (ET-1) (83) and vasoconstrictor prostanoids (84), and by inhibiting nitric oxide synthase activity. Moreover, angiotensin II increases oxygen free-radical production via membrane-bound NADH/NADPH oxidases (85). In the presence of ARBs, which selectively block AT1 receptors, angiotensin II can bind to unblocked AT2 receptors (86), which may stimulate nitric oxide synthesis (87). ARBs therefore theoretically should be superior to ACE inhibitors in restoring normal endothelial function. Although ACE inhibitors are known to inhibit the degradation, and hence increase the plasma concentration, of bradykinin, an endothelium-dependent vasodilator, some experimental evidence suggests that AT1 receptor antagonists, too, can activate the bradykinin system (88).

Effect of ACE inhibitors and ARBs on endothelium-dependent vasodilation in humans: Studies in patients with essential hypertension

Studies in conduit arteries. In the coronary epicardial arteries from patients with essential hypertension but with no overt atherosclerosis, intravenous administration of perindoprilat (1 mg i.v.) restored the normal vascular response to the cold pressor test and flow-mediated dilation (89). We are aware of no similar studies with ARBs. In the peripheral circulation of hypertensive patients, 6 months' treatment with perindopril (2–4 mg daily), but not with telmisartan (40–80 mg daily), restored brachial artery flow-mediated dilation (90).

Studies in the microcirculation. Studies in subcutaneous small vessels demonstrated that 2 years', but not 1 year's, treatment with cilazapril improved, but did not normalize, the blunted response to acetylcholine (91,92). Similar results were obtained by 3 years' treatment with lisinopril (93). In contrast, 1 year's treatment with losartan fully restored the vasodilatory effect of acetylcholine (94).

All studies assessing the effect of ACE inhibitors or ARBs in the forearm microcirculation have been negative. Two months' treatment with captopril or enalapril (95), 5 months' treatment with cilazapril (96) or 1 year's treatment with lisinopril (97) induced no change in the impaired response to methacholine or acetylcholine. On the other hand, in the group of hypertensive patients enrolled in one of these trials, lisinopril increased the vasodilatory response to bradykinin (98). However, the increased bradykinin-induced vasodilation was related to an ouabain-sensitive pathway, possibly hyperpolarization, rather than to restoration of nitric oxide availability (98). Similarly, treatment with candesartan (98) or valsartan (99) failed to improve acetylcholine-induced vasodilation in the forearm microcirculation of patients with essential hypertension.

The available evidence indicates that AT1 antagonists and ACE inhibitors are similarly effective in reversing endothelial dysfunction, with the more convincing effect being observed in the conduit artery of patients with coronary artery disease. Although ACE inhibitors seem more effective in the brachial artery of patients with essential hypertension, this finding is confined to one study. Both drug classes are effective in the subcutaneous, but not in the forearm, microcirculation, although ACE inhibitors can at least potentiate the vasodilation to bradykinin, an effect which is not mediated, however, by the restoration of NO availability.

Preserving cognition

Another important aspect of treating hypertensive patients with ACE inhibitors and ARBs is their potential to prevent cognitive decline and even to improve cognitive function. This effect, which has been demonstrated in animal models, is specific to agents that inhibit the renin–angiotensin system and is related to the negative effects of brain angiotensin II and its fragments on learning and memory paradigms (100). In the SCOPE study, the proportion of patients who had a significant decline or developed dementia was similar in the candesartan and placebo arms (46). However, in a recent study valsartan, but not enalapril, significantly improved cognitive function in patients with essential hypertension (101).

Metabolic syndrome and diabetes

Prognosis in hypertension is directly related to blood pressure reduction. Even small reductions in blood pressure are associated with large reductions in cardiovascular risk, especially in hypertensive patients with additional cardiovascular risk factors and, in particular, diabetes mellitus (102). This reinforces the need to determine the optimal blood pressure reduction for patients with type 2 (non-insulin-dependent) diabetes.

There is also a need to target people without overt diabetes but in whom hypertension is accompanied by disturbed glucose and insulin metabolism, i.e. the metabolic syndrome (103,104). There is much evidence showing that these subjects are at increased risk of cardiovascular disease and premature all-cause mortality as well. Moreover, the finding that the metabolic syndrome and hypertension often co-exist has increased interest in avoiding the adverse metabolic effects of antihypertensive agents that could precipitate the development of new-onset diabetes during long-term treatment (102). The cardiovascular risk associated with new-onset diabetes appears similar to that observed in patients diagnosed with type 2 diabetes at baseline, given a sufficiently long follow-up (106,105). ARBs have been shown to prevent the development of new-onset diabetes when compared with diuretics and beta-blockers in long-term studies in hypertensive patients, including LIFE (45) and SCOPE (46). Similar results have been obtained during ARB therapy in patients with heart failure (74,107). In the recent VALUE trial (41), patients in the valsartan arm had 23% fewer cases of new-onset diabetes compared with those with amlodipine: 13.1% vs 16.4%, respectively ($p < 0.0001$).

Type 2 diabetes. A recent review of antihypertensive therapy in type 2 diabetic patients found that, in most trials analysing cardiovascular outcome, most patients were on two-, three-, or even four-drug therapy (102). This is also true in trials comparing ARBs with other therapies, such in the substudy of diabetic patients in LIFE (Losartan Intervention For Endpoint reduction in hypertension study) (108), RENAAL (Reduction of End points in NIDDM (non-insulin-dependent diabetes mellitus) with Angiotensin II Antagonist Losartan) (44) and IDNT (Irbesartan Diabetic Nephropathy Trial) (43). The LIFE study showed a consistently significant reduction of major cardiovascular events, cardiovascular death and total mortality when losartan was compared with a beta-blocker (108). Similar positive effects for non-fatal cardiovascular events were also observed in a meta-analysis of ARB trials (109) that included data from RENAAL, IDNT and IRMA-2 (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study II) (51). In addition, data from the LIFE study indicate that losartan affords better protection than atenolol from cardiac death from arrhythmia (110). These data suggest a greater protective effect not only on the kidney but also on the cardiovascular system in patients with type 2 diabetes.

Metabolic syndrome. Strict blood pressure control is also necessary in patients with hypertension and the metabolic syndrome and there is a strong rationale for including an ARB in the combination therapy that most of these patients need (112).

Angiotensin receptor blockade improves insulin sensitivity in animal models of insulin resistance (113) and in humans (114,115). Furthermore, irbersartan and telmisartan have been shown to enhance PPARγ activity, which may represent new pleiotropic actions of ARBs, providing a potential mechanism for their insulin-sensitizing/antidiabetic effects (116,117). This contrasts with the disturbances in glucose metabolism associated with other antihypertensive agents and which may worsen long-term outcome (102). Thus, an improvement in insulin sensitivity with ARB therapy could be the main mechanism impeding or retarding the appearance of new-onset diabetes.

In conclusion, the cardiovascular protective effects of ARBs appear to be at least as good as those of ACE inhibitors in patients with the metabolic syndrome or type 2 diabetes.

Conclusions

The available data demonstrate that ARBs contribute to improving the prognosis of patients with cardiovascular and/or renal disease and appear to provide clinical benefit across the risk spectrum and regardless of the stage of disease. These benefits are facilitated by the long-term adherence of the patients to ARBs due to their excellent tolerability similar to that of placebo.

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