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REVIEW

Angiotensin-II receptor blockers: benefits beyond blood pressure reduction?

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Effective treatment of hypertension is essential to reduce the risk of renal and cardiovascular (CV) morbidity. The risks associated with hypertension are modulated by the presence of other factors. This has prompted the quest for agents that have benefits beyond blood pressure (BP) lowering. The angiotensin II receptor blocker (ARB) class of antihypertensive agents represents an important addition to the therapeutic options for elevated BP. Their ability to control BP is equivalent to existing therapies and there is a considerable and mounting evidence-base for their ability to reduce hypertension-associated target organ damage and comorbidities. Studies show that ARBs have clinical benefits across the spectrum of disease severity. In particular, recent large studies have demonstrated that these benefits extend to patients with conditions predisposing to CV events, such as diabetes, left ventricular hypertrophy and microalbuminuria, and where risk factors coexist. Data from these studies suggest that the CV protective effects of ARBs are at least, in part, independent from the BP lowering action. In addition, ARBs are extremely well tolerated, and strong evidence suggests that compliance with therapy — a key factor in achieving adequate BP control — with ARBs is higher than with other antihypertensive agents. Furthermore, flexible dosing and good tolerability profile mean that, where necessary, ARBs can be combined with other classes of antihypertensive agents to achieve adequate BP control and reduce the risk of hypertension-associated morbidity.
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Introduction

Elevated blood pressure (BP) is clearly and continuously related with cardiovascular (CV) morbidity and mortality. A recent meta-analysis has assessed the age-specific relevance of BP to cause-specific mortality. The study analysed information derived from about one million adults with no evidence of previous vascular disease.[1] The investigators found that throughout middle and old age, BP is strongly and directly related to vascular and overall mortality. Furthermore, there was no evidence of a threshold down to a BP of at least 115/75 mmHg.

Treatment of hypertension can prolong life, prevent or delay the development of heart failure and nephrosclerosis, and reduce the incidence of coronary events and stroke.[2] There is a direct relationship between the reduction in BP attained and the prognosis for hypertensive patients. Even small reductions in BP are associated with large reductions in CV risk, especially in hypertensive patients with additional CV risk factors such as diabetes.[3] However, there remains a divergence in survival rates between treated hypertensive and nonhypertensive men of similar age.[4] This poorer prognosis, even in the presence of active antihypertensive therapy, was observed in patients who were mainly treated with diuretics and β-blockers and followed for up to 23 years.[4]

Many factors, including the frequent, concomitant presence of risk factors including diabetes, late initiation of antihypertensive therapy and inadequate control of BP could account for the poorer prognosis observed in the hypertensive population. In particular, elevated levels of BP are associated with progressive target organ damage, which a late initiation of therapy cannot reverse. The different classes of antihypertensive drugs may have different capacities for organ protection. In particular, those

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agents that counteract the effects of angiotensin II (such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)) have been shown to be effective in reducing target organ damage in a series of different conditions.[5–11] In keeping with these properties of drugs blocking renin–angiotensin system (RAS) are the observations indicating that components of RAS, particularly renin, are recognised as population CV risk factors.[12]

Recently published guidelines have recognised the need for strict BP control in every hypertensive patient, but have also stressed that in some patient populations, such as those with diabetes or target organ damage, certain antihypertensive drugs may be more appropriate than others.[13,14] The established need for strict BP control contrasts with the poor achievements in clinical practice. Evidence suggest that less than one-third of patients attain the expected BP goal.[15] The underuse of combination therapy and a low compliance due to the adverse effects of drugs are among the most frequent causes of the failure to control BP.[16] Further factors may include a late initiation of therapy or the use of an inadequate antihypertensive regimen. The failure to address the different components of global CV risk could also play a role in the inadequate CV protection achieved in the hypertensive population.[17]

These factors lead to the conclusion that optimal vascular protection in arterial hypertension can only be achieved with earlier and tighter control of BP. Reaching this goal relies on the selection of the most appropriate therapy. For many patients, this may involve the use of agents that modulate the RAS. Evidence suggest that such agents, if dosage is appropriate, are as effective as the other classes of antihypertensive agents in achieving adequate BP control.[18]

Among the strategies that can interfere with the RAS, ARBs seem to have a selective mechanism of action[19] and the excellent tolerability of this class of agents results in better compliance and long-term adherence with treatment by patients.[20]

Antihypertensive efficacy of ARBs

Substantial reductions in diastolic and systolic BP can be achieved with ARB monotherapy or combinations of ARBs and any other class of antihypertensive agents, including diuretics, calcium channel blockers (CCBs), β-blockers, ACE inhibitors and β-blockers.[13,14] BP reductions with ARBs are equivalent to those obtained with all other first-choice antihypertensive drugs, although benefits of RAS-blocking agents may be linked to the fact that specific vascular beds (renal and cerebral) may be more sensitive to RAS-blocking agents than to other specific antihypertensive agents (eg β-blockers).[21] Normalisation or responder rates with ARBs alone or in combination with low-dose thiazide diuretics are similar to those obtained with the other first-choice antihypertensive classes, and there are no significant difference between the various ARBs in the BP lowering properties either in monotherapy or in fixed combination with diuretics. The most rational combination may be an ARB plus a low-dose thyazide diuretics (such as hydrochlorothiazide (HCTZ 12.5–25 mg)),[22] because this combination provides reciprocal amplification of BP lowering effects, while limiting the side effects of diuretics, which is particularly important for patients with metabolic disorders. The additional BP reduction provided by the combination with HCTZ is represented in Figure 1.[23] This example shows that the combination ARB valsartan plus hydrochlorotiazide regimen significantly reduced BP compared with ARB alone in hypertensive patients.[23] The additive efficacy of this regimen was confirmed in another study in which the BP control achieved with a combination of 160 mg/day valsartan and 12.5 mg/day HCTZ was improved when the dose of HCTZ component was increased to 25 mg/day.[24] Indeed, a therapeutic strategy based on the combination of ARB and low-dose thiazide diuretic is now extensively used in the clinical practice and it has been repeatedly used in large controlled studies.[9,10,22,25]

In these studies, combination of ARBs with thiazide diuretics was often required to achieve the target BP (usually $<140/90$ mmHg) (eg in the LIFE Study,[8] 91% of the patients were on combination therapy) and the interpretation of the effects on outcomes is related to this therapy rather than to the effect of monotherapy.

Long-term intervention studies with ARBs confirm the need for prompt and effective control of BP, in order to reduce the incidence of CV and renal events. In this regard, the uptitration of ARBs has been supplemented by the addition of a thiazide diuretic to achieve effective and long-term BP control.[9,10,22,25] The recently publication of the VALUE Study[22] comparing strategies based on valsartan or amlodipine has confirmed the need of BP control in high-risk patient, comparing strategies based on valsartan or amlodipine. In both arms, the combination therapy with a diuretic or additional other drugs was required in 64–73% of patients.

CV and renal protection with ARBs

In addition to effective BP control, ARBs appear to be able to provide additional benefits in hypertensive patients. The RAS plays a crucial role in circulatory homeostasis, and in patients with atherosclerosis, diabetes or hypertension, angiotensin II can contribute to the development and progression of disease. A high renin profile is an independent risk factor for CV disease in patients with hypertension and this CV risk is particularly significant in patients with concomitant diabetes.[26] Figure 2

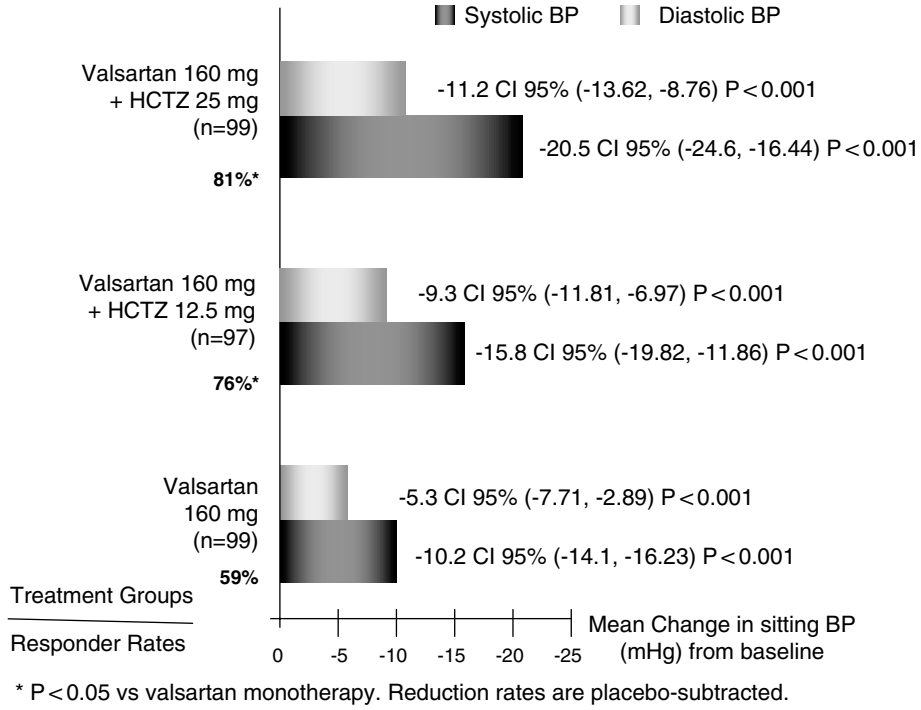

Figure 1 Effect of valsartan plus hydrochlorothiazide: high dose-related efficacy. Modified from Benz *et al*.[21]

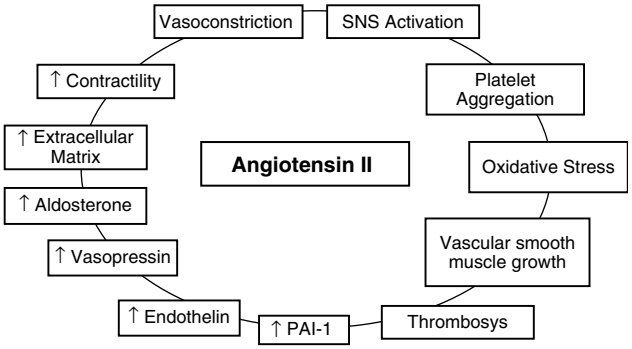

Figure 2 Pathophysiological effects of angiotensin II. Modified from Burnier and Brunner.[45]

summarises *how* the pathophysiological effects of angiotensin II that potentially *can* lead to CV events. In general, both the endocrine and the autocrine/paracrine effects on angiotensin II, including vasoconstriction, enhanced susceptibility to thrombosis, superoxide production, vascular smooth muscle growth, myocyte hypertrophy, fibrosis, remodelling of tissues and stimulation of a number of other hormonal mediators, represent solid candidate mechanisms driving CV and renal pathology.[27]

The most effective ways of blocking the RAS is to use ACE inhibitors or ARBs, with ARBs selectively blocking the interaction between angiotensin II and the AT1 receptor. This selectivity may be important because the interaction between *residual, unbound* angiotensin II and the AT2 subtype receptors may result in an amplification of the beneficial effects of AT1 blockade, and may favour vasorelaxation, and *reduced* development of hypertrophy and cardiovascular remodelling.[28]

Blocking the RAS with ACE inhibitors or ARBs has been indeed shown to reduce CV end points in a variety of conditions including hypertension, type 2 diabetes, stroke, renal disease, heart failure, left ventricular dysfunction (LVD), acute myocardial infarction (MI) and coronary artery disease (CAD) (Table 1). The clinical experience with ARBs is increasing with approximately 100 000 patients involved in *completed* or ongoing clinical trials (Table 2). This extensive clinical experience will clarify the positioning of ARBs in the treatment of hypertension, CV disease, diabetes and nephropathies.

A first and strong evidence that ARBs have effects on CV risk that are independent of BP reductions came from the Losartan Intervention For Endpoint (LIFE) study.[8] In LIFE Study,[8] which recruited more than 9000 patients with hypertension and left ventricular hypertrophy, the treatment regimen based on the ARB losartan produced similar BP reductions to the treatment regimen based on the β-blocker atenolol (final BP of 144.1/81.3 *vs* 145.4/80.9 mmHg, respectively). However, the losartan-based regimens reduced the risk of the combined end point of CV death, stroke and MI by 13% ($P=0.021$) compared with atenolol-based regimens (Figure 3) and reduced the incidence of fatal and nonfatal stroke by 25% compared with atenolol. Beneficial effects of losartan on CV outcomes that could not be ascribed to BP reductions were also

Table 1 Proven benefits by blocking the renin–angiotensin system

Patient type	*Evidence of benefit*			*Drug*
Hypertension[a]	↓ Mortality	↓ Heart failure	↓ Ischaemic events	ACE-I, ARB
Hypertension/LVH	CV composite EP		Stroke	ARB
Hypertension, elderly	CV Composite EP			ACE-I,ARB
High-risk patients	↓ Mortality	↓ Heart failure	↓ Ischaemic events	ACE-I, ARB
CAD without LVD	↓ Mortality	↓ Heart failure	↓ Ischaemic events	ACE-I
Acute MI	↓ Mortality	↓ Heart failure		ACE-I, ARB
LVD	↓ Mortality	↓ Heart failure	↓ Ischaemic events	ACE-I, ARB
Heart failure	↓ Mortality	↓ Heart failure	↓ Ischaemic events	ACE-I, ARB
Renal disease	↓ ESRD/mortality	↓ Heart failure	↓ Ischaemic events	ACE-I, ARB
Stroke	↓ Mortality		↓ Ischaemic events	ACE-I, ARB
Type 2 diabetes+kidney disease	Primary end points			ACE-I, ARB

[a]Hypertension with LVD or DM.

Table 2 Concluded and ongoing trials with angiotensin II receptor blockers

	Losartan	*Valsartan*	*Irbesartan*	*Candesartan*	*Telmisartan*
Hypertension	LIFE[a] (9.193)	VALUE[a] (15.314)	—	SCOPE[a] (4.000)	ONTARGET (23.400)
Heart failure	ELITE II[a] (3.152)	Val-HeFT[a] (5.010)	I-PRESERVE (~3.000)	CHARM[a] (7.600)	—
Post MI	OPTIMAAL[a] (5.000)	VALIANT[a] (14.500)	—	—	—
Nephropathy	RENAAL[a] (1.513)	ABCD-2V (⩾620)	IDNT[a] (1715) IRMA2[a] (590)	—	—
IGT	—	NAVIGATOR (7.500)	—	—	—
TOTAL	18.858	~43.000	~5.300	11.600	23.400

[a]Completed trial.

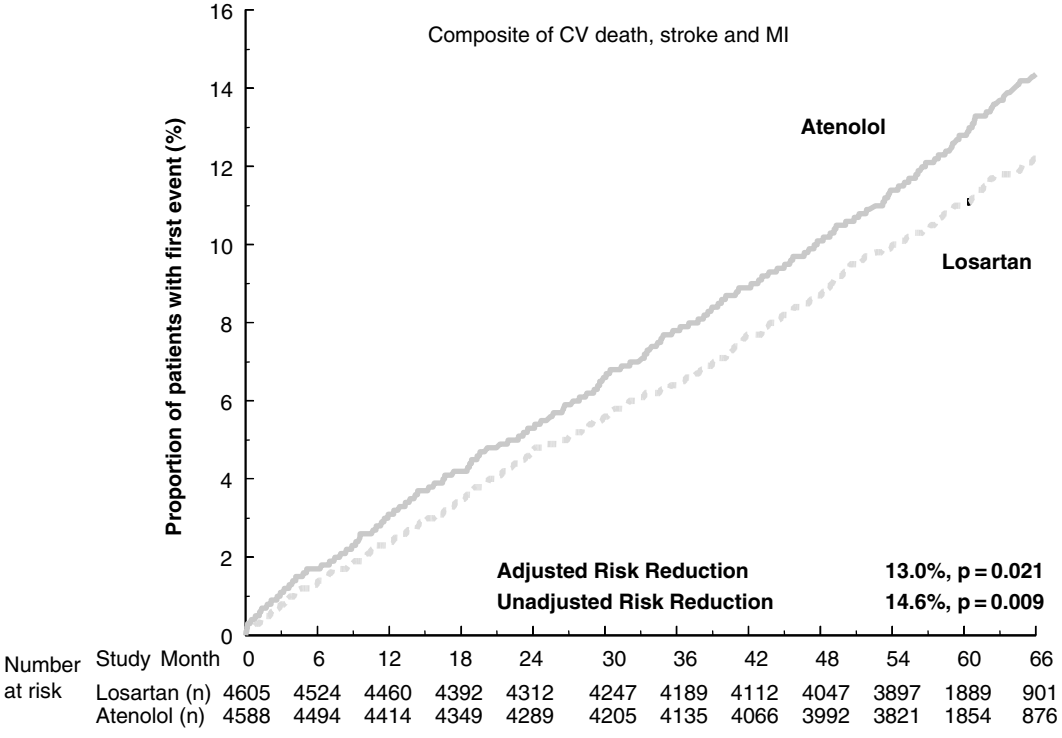

Figure 3 Effect of losartan on primary composite end point (cardiovascular death, stroke and myocardial infarction): results from the LIFE Study.[a]

observed in patients with isolated systolic hypertension and in diabetes.[29,30]

In the VALUE Study,[22] which compared strategies based on amlodipine and valsartan in more than 15 000 high-risk patients, in spite of a significantly higher BP reduction in the amlodipine arm, there was nonsignificant difference in the combined primary end point. In addition, the analysis of the components of the combined end points also showed that the difference in favour of amlodipine were largely accounted for by the larger and earlier reduction obtained with the CCB (Figure 4). This emphasises the need to *adequately* and rapidly titrate ARBs in patients with hypertension and to consider the utilisation of the combination with low-dose thiazide diuretic as a first step of the therapy in the high-risk patients, in agreement with suggestions from the most recent guidelines.[13,14] In this regard, detailed analysis of the VALUE results showed that the BP differences between amlodipine and valsartan in the VALUE Trial[22] were quite large during the first couple of months of treatment. It was during this early part of the trial that most of the excess events in the valsartan group occurred.[31] In fact, when patients were matched for identical achieved BPs, events if anything tended to be slightly less in the valsartan group, particularly for heart failure and diabetes.[32]

An additional benefit of RAS-blocking treatment regimens is the lower incidence of new onset diabetes compared with diuretic, β-blocker, or CCBs-based regimens (Table 3). This has been shown in a number of trials including The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[33] the LIFE study[8] and the Captopril Prevention Project (CAPPP),[34] and more recently in a convincing analysis of the VALUE Study,[22] which compared the ARB valsartan with amlodipine. In the latter study, patients receiving the valsartan therapy developed less (about 23%) new onset diabetes as compared with the patients receiving amlodipine.[22] This property of ARBs is particularly relevant to the subsequent development of CV and renal disease. In fact, recent studies[35,36] show that new onset diabetes during long-term antihypertensive treatment is associated with poor prognosis. In addition to that, it is well known that development of diabetes in hypertension accelerates renal impairment and evolution towards end-stage renal disease. This favourable impact of the drugs inhibiting the RAS, and particularly ARBs, on development of diabetes is attributable to specific mechanisms[37] associated with angiotensin II blockade,[38] and cannot be accounted for only by the detrimental metabolic effects of the comparators (diuretics, β-blockers, CCBs).

Renal protection is another important goal of therapy in diabetes, hypertension and atherosclerotic diseases, and has a significant influence on the overall prognosis of patients. Blocking the RAS represents a successful strategy to slow the progression of renal impairment in these diseases, and this has been confirmed in three large clinical trials with ARBs in diabetic nephropathy.[9,10,25,39]

The Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA 2) trial[25] showed that ARBs delay the progression from microalbuminuria to macroalbuminuria. In addition, ARBs delayed progression from macroalbuminuria to end-stage renal disease in the Irbesartan Diabetic Nephropathy Trial (IDNT)[9] and the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study.[10] The Microalbuminuria

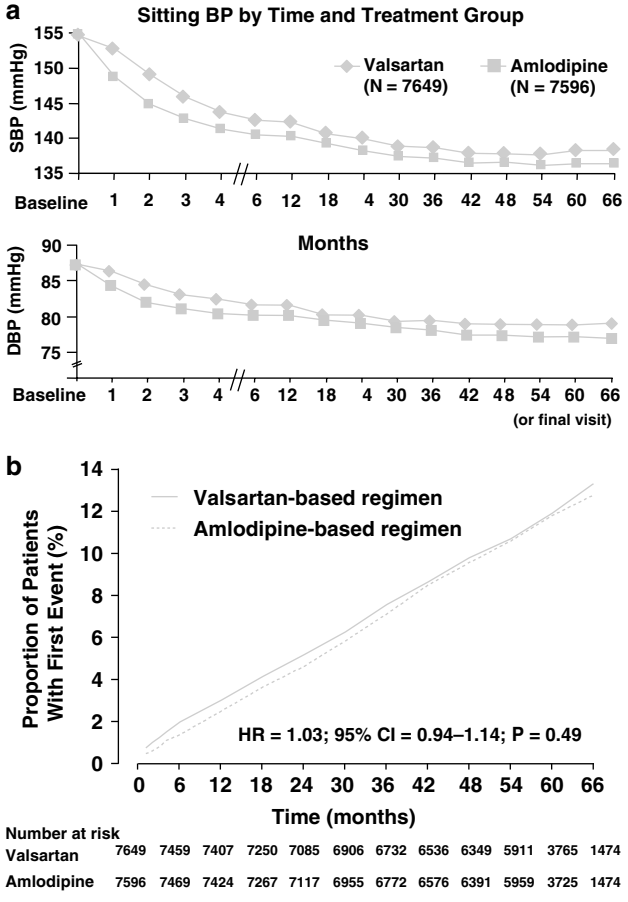

Figure 4 Blood pressure levels (panel a) and primary composite cardiac endpoint (panel b) in the VALUE Study. Modified from Julius *et al*.[20]

Table 3 Reduction of new onset of diabetes with drugs blocking the renin–angiotensin system

ALLHAT	Chlortalidone (11.6%)	Lisinopril (8.1%)	−30%
LIFE	Atenolol (8%)	Losartan (6%)	−25%
HOPE	Chlortalidone (5.4%)	Ramipril (3.6%)	−33%
CAPPP	BB/Diur	ACEi	−21%
CHARM	CT (7%)	Valsartan (6%)	−22%

Reduction with Valsartan (MARVAL) study[39] extended this observation, proving that with a strictly similar BP level, valsartan differed from amlodipine in its capacity to significantly reduce microalbuminuria excretion. This finding again suggests that properties of ARBs, which go beyond BP control, are relevant to CV and renal protection. In fact, the reduction of microalbuminuria and of its progression to overt proteinuria has been associated with a lower CV morbidity and mortality in a LIFE substudy.[40]

The most recent management guidelines[13,14] accept these new findings and recommend the early inhibition of RAS particularly in patients with nephropathy, ARBs are advised as the first choice in patients with type 2 diabetes.

Blocking the RAS has also benefits in patients with heart failure on LVD. In the Valsartan Heart Failure Trial (Val-HeFT),[41] the addition of valsartan to standard therapy for heart failure, *including ACE-inhibitors and β-blockers*, reduced the risk of total mortality or hospitalisation by 13% ($P=0.009$) compared with placebo. The benefits of ARBs in patients with heart failure were recently confirmed in the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) programme. In the CHARM-Alternative arm[42] (ARBs used as an alternative to ACE inhibitors in patients who could not take ACE inhibitors), candesartan at a target dose of 32 mg daily reduced the risk of CV death or congestive heart failure (CHF) hospitalisation by 23% ($P=0.0004$) compared with placebo. Furthermore, in the CHARM-Added arm[43] (ARBs added to ACE inhibitors as combination therapy), candesartan reduced the risk of CV death or CHF hospitalisation by 15% ($P=0.011$) compared with placebo. The outcome trends were favourable for ARBs also in the 'Preserved' arm, that is, in patients with preserved left ventricular function, which included about 64% with hypertension.[44] Overall, candesartan conferred benefit to heart failure patients by reducing CV death by 12% ($P=0.012$) without influencing non-CV death.[45] These data are strong enough to suggest a role for ARBs as alternatives or additions to ACE inhibitor regimens in patients with heart failure.

Finally, results from the Valsartan in the Acute Myocardial Infarction Trial (VALIANT)[46] show that valsartan was as effective at reducing mortality as the ACE inhibitor captopril in patients who are at a high risk of CV events after myocardial infarction and LVD or heart failure. A combination of the two agents did not improve mortality.

The evidence that ARBs can have benefits at any stage of the CV disease continuum—from patients with risk factors such as diabetes and hypertension, to patients with atherosclerosis and LVD, and even post-MI—emphasises potential beneficial effects of these agents, which are independent of BP control, in a wide variety of patients at risk of CV disease.

Safety and tolerability of ARBs

The increasing use of ARBs as first-line agents in hypertension and other patients at risk of CV disease is based not only on the BP efficacy described above but also on the *excellent* tolerability of this class of drugs. The tolerability of ARBs has been assessed in a variety of patient groups such as patients with hypertension, diabetes, renal disease, CHF and post-MI.

It has been repeatedly and convincingly shown that the number of discontinuations due to adverse events in hypertensive patients receiving ARBs is not significantly different to the number obtained in subjects receiving placebo. The most frequently observed adverse events with ARBs are occasional headache and dizziness, which can be reduced by lowering the dose of drug[20] and may not be specifically related to the drugs.

In the Val-HeFT population[41] (heart failure and LVD), the addition of valsartan caused only small increases in discontinuations (9.9 *vs* 7.2% with placebo), dizziness (1.6 *vs* 0.4%) and renal impairment (1.1 *vs* 0.2%). Similarly, in the CHARM programme,[45] also in patients with heart failure, the addition of the ARB candesartan increased adverse events by relatively small amounts compared with placebo; the incidence of any adverse event or laboratory abnormality was 21.0 and 16.7% for candesartan and placebo, respectively.

In the VALIANT Study,[46] in patients who had experienced an MI, the adverse events leading to discontinuation were similar in the valsartan recipients to those in the captopril recipients—but the overall rate of discontinuation due to adverse events was lower in the valsartan group. Hypotension was more frequent in patients receiving the ARB, and cough, skin rash and taste disturbance were more frequent in patients receiving the ACE inhibitor. Adverse events were additive in patients who received an ARB and an ACE inhibitor. Also in the trials performed in patients with renal disease, such as IDNT[9] and RENAAL,[10] the excellent tolerability of ARBs was substantially confirmed.

An important aspect of any antihypertensive drug, which relates to both efficacy and tolerability, is the effect on the patient's quality of life. In general, stricter BP control appears to be associated with improved mood in patients with hypertension.[3] Evidence for the effects of ARBs on quality of life came from the MICCAT study.[47] Using the general well-being index to measure quality of life, telmisartan monotherapy improved quality of life in hypertension patients regardless of whether they had previous treatment and whether that treatment was effectively controlling their BP. The effects of telmisartan on quality of life were at least as good as those achieved by aggressive BP control in the Hypertension Optimal Treatment (HOT) study.[3] The improvement in quality of life observed with ARB treatment is consistent across different groups

of patients; for example, in patients below 65 years of age and above 65 years of age, and in different races.[20] Interestingly in Val-HeFT,[41] treatment with valsartan halted the deterioration in the quality of life seen in placebo recipients during the course of the trial, suggesting that the quality of life benefits of ARBs are consistent across a variety of patient groups.

The favourable *tolerability* profile of ARBs and their effects on quality of life appears to result in higher continuation of the drugs by patients at 1 and 4 years compared with other classes of antihypertensive drugs (Figure 4). Furthermore, the use of fixed combinations of ARB + HCTZ has increased from around 20% in 1998 to 40% in 2003, probably reflecting greater recognition by the doctor of the need of combination therapy to control BP and excellent acceptance by the patient of fixed-dose combinations.

Conclusion

The data reviewed in this paper show the potential of ARBs to contribute to the improved prognosis of CV disease. Studies suggest that ARBs can provide clinical benefit across the spectrum of CV risk, from the control of CV risk factors, mostly high BP, to the early stages of CV disease and/or renal damage, through to patients in whom CV disease is already present, as shown by the results of different studies.[8–10,22,23,25,41–46] In many of these studies, the benefits of ARBs on outcome cannot be strictly attributed to the BP lowering effect and suggest that ARBs may improve prognosis through effects independent of BP reduction. ARBs seem to confer protection independent from blood pressure on a number of important intermediate end points, which are related to subsequent development of CV events, such as left ventricular hypertrophy,[8] microalbuminuria,[9,25,39,40] new-onset of diabetes,[30] and doubling of creatinine.[9,25] This aspect should be further investigated in specifically designed trials.

These data prompt the discussion of two issues of great clinical relevance. Firstly, the data suggest that ARBs are to be considered an appropriate therapy for patients with arterial hypertension regardless of the stage of disease. The capacity of ARBs to reduce BP is that of any other class of antihypertensive agent, and there is a considerable evidence base for their ability to provide protective effects beyond BP control for the heart, brain and kidney. The guidelines[13,14] emphasise that early initiation of therapy is mandatory. Furthermore, maximal reduction of CV risk relies on the identification of those at high risk and the integration of appropriate antihypertensive therapy with a comprehensive pharmacological approach to address all CV risk factors. In addition, the properties of ARBs favour their combination with all the antihypertensive classes, as is often necessary to achieve BP goals, according to guidelines.[13,14] The second issue of clinical relevance is that the unsurpassed tolerability of the ARB class will facilitate the long-term compliance and adherence to therapy, thus facilitating the simultaneous protection of the renal and CV systems.

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Appendix

Potential Conflict of Interest

All authors have given lectures for industries producing ARBs.