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Benefits of angiotensin-II receptor blockers. Are we going beyond blood pressure control?

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ABSTRACT

Despite the well-known relationship between high blood pressure levels and increased rate of cardiovascular mortality and morbidity, blood pressure control remains poorly achieved. In addition, hypertension is closely related and associated with other cardiovascular risk factors, target organ damage or diabetes, thus hypertensive patients are exposed to a higher level of risk for major cardiovascular events. Thus, effective treatment of hypertension and prevention of its complication remains a cornerstone of cardiovascular prevention.

In this regard, recent clinical studies have demonstrated that drugs inhibiting the Renin-Angiotensin System, particularly Angiotensin II Receptor Blockers (ARBs), confer clinical benefits across the spectrum of cardiovascular disease, from patients with conditions predisposing to cardiovascular events, such as left ventricular hypertrophy, microalbuminuria and diabetes mellitus, to patients with coronary artery disease or stroke, congestive heart failure and end-stage renal disease. Data from these studies suggest that the cardiovascular protection achieved by ARBs is at least, in part, independent from the blood pressure lowering effect. Furthermore, this class of drugs is extremely well tolerated, thus providing higher compliance than that obtained with other antihypertensive agents.

Benefits beyond blood pressure lowering effect and good tolerability profile also make ARBs as a key component of combination therapy with other classes of antihypertensive agents to achieve adequate blood pressure control and reduce the risk of incidence of cardiovascular and renal events in hypertensive patients.

KEY WORDS

Angiotensin II receptor blockers, antihypertensive therapy, blood pressure, cardiovascular risk, hypertension.

INTRODUCTION

Observational studies have shown a significant and continuous relation between high blood pressure levels and increased incidence of cardiovascular mortality and morbidity[1-5]. Effective treatment of hypertension significantly reduces the incidence of coronary events and ischemic stroke, and prevents the development or delays the progression of atherosclerotic disease to congestive heart failure and end-stage renal disease[6-9]. In fact, there is a close relationship between the reduction in blood pressure attained and a better prognosis for hypertensive patients: even small reductions in blood pressure levels are associated with large reductions in cardiovascular risk, especially in hypertensive patients at high-risk, such as those with target organ damage or diabetes[10]. However, recent observational data showed that even in the presence of antihypertensive treatment, mainly based on diuretics and Beta-Blockers (BB),

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hypertensive patients, followed for up to 23 years, have lower survival rates than non-hypertensive ones, matched for age and sex[11]. Together with other observations, these data suggest that other factors, beyond blood pressure levels, influence the prognosis in hypertensive patients.

Many factors, including the frequent concomitant presence of multiple risk factors such as metabolic syndrome, diabetes, dyslipidemia, central obesity, could account for the poorer prognosis observed in the hypertensive population[12,13]. In addition, hypertension has shown a strong correlation with target organ damage and associated clinical conditions, which contribute to confer a higher level of cardiovascular risk to develop major cardiovascular events[14,15]. In this regard, recent guidelines for management of arterial hypertension have underscored the need for lowering blood pressure at target levels, especially in those patients with high-risk profile, independently of the class of antihypertensive agents used to achieve these goals[16-18].

However, this issue represents a debated aspect in the proper management of arterial hypertension. In fact, different classes of antihypertensive drugs may have different capacities for realizing target organ protection[19-21]. In particular, those agents that counteract the effects of the activation of the Renin-Angiotensin System (RAS), particularly Angiotensin-Converting Enzyme Inhibitors (ACE-Is) and Angiotensin II Receptor Blockers (ARBs), have been shown to be effective not only in reducing blood pressure levels, at a degree comparable to the other traditional antihypertensive agents[16-18], but mostly in preventing the occurrence or in delaying the progression of target organ damage in a series of different conditions[19]. The most recent guidelines have recognized the need for strict blood pressure control in each hypertensive patient with the major purpose of reducing growing incidence of cardiovascular disease in the overall population, but these documents have also stressed that in particular subgroups oh hypertensive patients, such as those with target organ damage or diabetes, specific antihypertensive drugs may be more appropriate than others, thus suggesting the existence of "compelling indications" that may represent a strategic priority in the management of hypertension[16-18].

The established need for strict blood pressure control, documented in the clinical trials, strongly contrasts with the poor achievements in clinical practice. Observational studies, in fact, suggest that less than one-third of patients achieved blood pressure target levels[5]. 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 blood pressure control[22,23]. Further elements may include a late initiation of therapy or the use of an inadequate antihypertensive regimen. The failure to address the different components of global cardiovascular risk could also play a role in the inadequate cardiovascular protection achieved in the hypertensive population[22,23].

These factors lead to the conclusion that effective cardiovascular protection in hypertension can only be achieved with appropriate blood pressure control, through the selection of the most appropriate antihypertensive therapy in the individual hypertensive patient on the basis of its own cardiovascular risk profile[22-24]. In this regard, many hypertensive patients required combination therapy, often involving the use of agents that modulate the RAS, for achieving adequate blood pressure control and an effective organ protection with a better tolerability profile[16-18]. In particular, among the strategies that can interfere with the RAS, ARBs provide a very attractive option in view of the selective mechanism of action[25,26], and of the excellent tolerability, which results in better compliance and long-term adherence to treatment[27,28].

ANTIHYPERTENSIVE EFFICACY OF ARBS

Recent guidelines in hypertension have confirmed that significant reductions in both diastolic and systolic blood pressure levels can be achieved with any class of antihypertensive agents, including diuretics, Calcium Channel Blockers (CCBs), BBs, ACE-Is and ARBs, either in monotherapy or mostly in combination therapy[16-18]. In particular, blood pressure reductions obtained with the newer antihypertensive agents, including ARBs, are equivalent to those obtained with all other classic first-choice antihypertensive drugs[16-18], although benefits obtained by RAS blockade may theoretically add further benefits, due to the fact that renal and cardiovascular protective effects have been described with RAS blocking agents[29-31]. In addition, 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 differences between the various ARBs in the blood pressure lowering effects at the tested dosage[32].

In this latter regard, the most rational combination may be an association between an ARB plus a low-dose thyazide diuretics[33,34], because this combination provides reciprocal amplification of blood pressure lowering effects, while limiting the side effects of diuretics, which is particularly important for patients with metabolic disorders. 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, in which the up-titration of ARBs has been supplemented by the addition of a thiazide diuretic to achieve effective and long-term blood pressure control[33,34]. In these studies combination of ARBs with thiazide diuretics was often required to achieve the target blood pressure, as reported in the Losartan Intervention For End-point

reduction in hypertension (LIFE) study[33], in which 91% of the patients were on combination therapy, or in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) randomised trial[34], in which the combination therapy with a diuretic or additional other drugs was required in 64% - 73% of patients.

Cardiovascular and renal protection with ARBs

Several and different lines of evidence suggest that ARBs appear may provide additional benefits in hypertensive patients[19]. In this regard, the final effector of RAS, Angiotensin II, is a major player in development and progression of cardiovascular disease[35-39]. Experimental studies have demonstrated that a high renin profile is an independent risk factor for cardiovascular disease in patients with hypertension and this cardiovascular risk is particularly significant in patients with concomitant diabetes[40,41]. 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 the development of cardiovascular and renal pathology[25,26]. The most rational way of blocking the RAS is to use ARBs, which selectively blocks the interaction between angiotensin II and the AT1 receptor. This selectivity is also 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[25,26].

The clinical experience with ARBs is increasing with approximately 100000 patients being involved in completed or ongoing clinical trials[33,34,42-70]. Blocking the RAS with ACE-I or ARBs has been indeed shown to reduce cardiovascular events in different settings, including hypertensive patients at high-risk or left ventricular hypertrophy[33,34,55,65,70], ischemic stroke[33,56], acute myocardial infarction and coronary artery disease[43,46-49,63,64,66,69], congestive heart failure with left ventricular dysfunction[42,45,51,53,54,60,67], type 2 diabetes and diabetic renal disease[50,57-59,61,68].

A very strong and convincing evidence that ARBs have effects on cardiovascular risk that are independent of blood pressure reductions can be derived from the LIFE study[33], which recruited more than 9000 patients with hypertension and left ventricular hypertrophy. Treatment regimen based on the ARB losartan produced quite comparable blood pressure reductions to the treatment regimen based on the BB atenolol, however, the losartan-based regimen reduced the risk of the primary composite endpoint (cardiovascular death, stroke and myocardial infarction) compared with atenolol-based regimen[33]. In particular, losartan significantly reduced the incidence of fatal and non-fatal stroke compared with atenolol in hypertensive patients with left ventricular hypertrophy[33]. Further studies of the LIFE population have demonstrated beneficial effects of losartan-based regimen on cardiovascular outcomes beyond blood pressure reductions, in patients with isolated systolic hypertension[71], left ventricular hypertrophy[72], atrial fibrillation[73,74], microalbuminuria and renal impairment[75-77] and diabetes mellitus[78]. In particular, analysis of LIFE population also shows the ability of the ARB losartan to prevent new development of atrial fibrillation[73,74] and diabetes mellitus[78], independently of the blood pressure lowering effect.

NEW FRONTIERS FOR CARDIOVASCULAR PROTECTION

Prevention of new-onset diabetes and diabetic nephropathy

The lower incidence of new onset diabetes achieved with ARBs has been observed in comparison with diuretic, BB, or CCB based regimens[79]. Recent studies demonstrated that new onset diabetes during long-term antihypertensive treatment is associated with poor prognosis in hypertensive patients[80,81], and it is well known that development of diabetes in hypertension accelerates renal impairment and evolution towards end-stage renal disease[82,83]. This favourable impact of the drugs inhibiting the RAS, and particularly ARBs, on development of diabetes, is attributable to specific mechanisms associated with angiotensin II blockade[50,57-59,61,68,75-77], and cannot be accounted for only by the detrimental metabolic effects of the comparators (diuretics, BBs, CCBs)[84,85].

Recent intervention trials in patients with type 2 diabetes and hypertension have clearly and consistently demonstrated the efficacy of ARBs particularly irbesartan[57,58], valsartan[61], losartan[59,33,75-77] and telmisartan[68] in limiting the progression of renal failure as compared to conventional treatment or calcium antagonists. In this regard, the Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA2) trial showed that ARBs delay the progression from microalbuminuria to microalbuminuria[58], whereas the Irbesartan Diabetic Nephropathy Trial (IDNT)[57] and the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study[59] demonstrated that ARBs delayed progression from macroalbuminuria to end-stage renal disease. The Microalbuminuria Reduction with Valsartan (MARVAL) study[61] integrated this observation, proving that in presence of similar blood pressure reduction, ARBs significantly reduced microalbuminuria excretion with respect to the comparator amlodipine. More recently, the reduction of microalbuminuria and of its progression to overt proteinuria has been associated with a lower cardiovascular morbidity and mortality in a LIFE sub-study[75-77]. Finally, the Diabetics Exposed

to Telmisartan And enalaprIL (DETAIL) Study Group, which compared the renoprotective effects of ARBs in subjects with type 2 diabetes and early nephropathy, demonstrated that telmisartan is not inferior to enalapril in providing renoprotection (reduced glomerular filtration rate) this kind of patients[68].

These observations may directly and further enhance the potential causal role of angiotensin II in the pathogenesis of microalbuminuria in diabetes and arterial hypertension, suggesting that properties of ARBs beyond blood pressure control are relevant to confer cardiovascular and renal protection. As a consequence, the most recent guidelines in the management of hypertension have accepted these new data and recommend the early inhibition of RAS, particularly in hypertensive patients with type 2 diabetes[16-18].

Prevention of new-onset atrial fibrillation

Although the mechanisms leading to Atrial Fibrillation (AF) are complex and not completely yet understood, a growing body of evidence accumulated over the past five years suggest that the RAS, particularly Angiotensin II, may play a crucial role in the pathogenesis of AF. Angiotensin II is a potent promoter of fibrosis, and atrial fibrosis, a frequent finding in hypertensive patients with AF, may lead to intra-atrial conduction disturbances and to persistent susceptibility to AF[86]. Increased ACE expression and changes in Angiotensin II Receptor subtypes expression occur in the atria of patients with AF. In this regard, Angiotensin II type 1 Receptor (AT1r) stimulation causes atrial hypertrophy and fibrosis, whereas Angiotensin II type 2 Receptor (AT2r) stimulation counteracts this effect. Due to the abnormal activation of RAS, patients with AF have reduced AT1r and increased AT2r density[87]. Furthermore, there is also evidence suggesting that both ACE and RAS polymorphisms play a role in predisposing patients to AF[88,89]. However, the strongest support for a major role of RAS in pathophysiology of AF derives from the growing evidence that drugs inhibiting RAS may prevent the new onset or delay recurrence of AF.

In this latter regard, recent data suggest that ACE inhibitors attenuate atrial remodeling in experimental models of AF[90], and significantly reduces the incidence of AF in patients with left ventricular dysfunction[86, 91]. In the Trandolapril Cardiac Evaluation (TRACE) study, the ACE inhibitor trandolapril reduced the incidence of AF by 47% after acute myocardial infarction in patients with left ventricular dysfunction[91]. In a retrospective analysis of patients from the Montreal Heart Institute included in the Studies Of Left Ventricular Dysfunction (SOLVD), the ACE inhibitor enalapril decreased the incidence of AF by 77% over a mean follow-up of 2.9 1.0 years[86]. Moreover, Ueng *et al.*[92] have reported that the addition of enalapril to amiodarone significantly decreased the rate of immediate recurrences and facilitated subsequent long-term maintenance of sinus rhythm after elective electrical cardioversion in patients with persistent AF.

More recent experimental data suggest that RAS inhibition by ARBs also prevents the promotion of AF by suppressing the development of electrical and structural cardiac remodeling[93]. In addition, Madrid *et al.*[94] have shown that pre-treatment with the ARB irbesartan could also reduce the recurrence of AF after electrical cardioversion in amiodarone-treated patients. Recently, two subgroup analyses of the LIFE study extend these observations and provide further evidence, in hypertensive patients with left ventricular hypertrophy, for the benefit of RAS inhibition, in the prevention of new-onset AF and in the reduction of cardiovascular morbidity and mortality associated with new-onset or persistent AF[73,74]. In the subgroup of patients with a history of AF or ECG-documented AF, as compared to atenolol-based therapy, losartan-based therapy reduced the primary composite end point of the LIFE study (cardiovascular mortality, fatal or nonfatal stroke, and fatal or nonfatal myocardial infarction) by 42% and the occurrence of stroke by 45% over 4.8 years of follow-up[73]. In patients in sinus rhythm at entry, losartan-based therapy reduced new-onset AF by 33% and subsequent stroke by 51% compared to atenolol-based therapy, despite similar blood pressure reduction. Patients who developed new-onset AF in the losartan group had 40% fewer primary composite end points and 51% fewer strokes than those in the atenolol group[74]. It is interesting to note that in the LIFE study, rates of myocardial infarction and hospitalization for angina pectoris were similar in patients treated with losartan and in those receiving atenolol[33], suggesting that RAS inhibition is perhaps as effective as beta-blockade in the prevention of acute coronary syndromes. Such a hypothesis requires further study. On the other hand, hospitalization for heart failure was less frequent, and there was a trend for fewer sudden cardiac deaths, with the atenolol versus the losartan regimen[33], indicating that both treatment modalities are complementary, not mutually exclusive, in hypertensive patients.

Preservation of left ventricular function

A large body of evidence also suggests that RAS blocking agents provide favourable effects in patients with heart failure and left ventricular dysfunction, independently by blood pressure lowering effect. In this regard, the first evidence derived from the Valsartan Heart Failure Trial (Val-HeFT), in which the addition of the ARB valsartan to standard therapy for heart failure, including ACE-Is and BB, reduced the risk of total mortality or hospitalisation for heart failure, compared with placebo[95]. More recently the beneficial properties of ARBs in patients with heart failure and left ventricular dysfunction were confirmed in the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity

(CHARM) programme, in which candesartan-based therapy significantly reduced cardiovascular death, either in addition or in alternative of ACE inhibition[96-98]. In this latter regard, in the CHARM-Alternative arm (ARBs used as an alternative to ACE-Is in patients who could not take ACE-Is), candesartan significantly reduced the risk of cardiovascular death or hospitalisation for heart failure[97], while in the CHARM-Added arm (ARBs added to ACE-Is as combination therapy) candesartan reduced the risk of cardiovascular death or hospitalisation for heart failure, compared with placebo[98]. Finally, in the CHARM-Preserved arm, which recruited patients with preserved left ventricular function, mostly with hypertension, the candesartan-based therapy resulted in a better outcome in term of reduction of cardiovascular mortality and incidence of non-fatal myocardial infarction and non-fatal ischemic stroke[99].

CONCLUSIONS

In conclusion, The evidence that ARBs may provide additional benefits at any stage of the cardiovascular disease continuum emphasizes the potential favourable effects of these agents, that are independent of blood pressure control, in a wide variety of patients at risk of cardiovascular disease or with cardiovascular or renal impairment[33,34,42-79]. The increasing use of ARBs as first-line agents in hypertension and other patients at risk of cardiovascular disease is based not only on the blood pressure efficacy described above[33], but also on the excellent tolerability of this class of drugs, which has been assessed in a variety of patient groups such as patients with hypertension, diabetes, renal disease, congestive heart failure and post myocardial infarction[33,34,42-78,95-99]. The favourable tolerability profile of ARBs and their effects on the quality of life appears to result in higher continuation of the drugs compared with other classes of antihypertensive drugs[27,28].

Clinical studies suggest that ARBs can contribute to the improved prognosis of cardiovascular disease and provide clinical benefit beyond blood pressure lowering effect and across the spectrum of cardiovascular risk, from the control of cardiovascular risk factors, in the early stages of cardiovascular disease and/or renal damage, and in the different stage stages of coronary artery disease and heart failure[33,34,42-78,95-99]. A large body of evidence demonstrates that the benefits obtained with ARBs-based antihypertensive regimen cannot be strictly attributed to the blood pressure lowering effect, suggesting that ARBs may improve prognosis through effects independent of blood pressure reduction[19]. In fact, ARBs seem to confer protection independent from blood pressure in a number of important intermediate end-points, which are related to subsequent development of cardiovascular events[33,34,42-78,95-99]. These data confirm that ARBs are to be considered an appropriate therapy for patients with arterial hypertension regardless of the stage of disease.

The properties of ARBs favours their combination with all the antihypertensive classes, as is often necessary to achieve blood pressure goals, accordingly to recent guidelines[16-18]. In addition, 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 cardiovascular systems. However, a number of other large clinical investigations are under way to confirm the current indications, but mostly to explore whether these compounds may be effectively used in other indications, such as in high-risk patients, in patients with metabolic syndrome, in patients with microalbuminuria, or even to prevent microalbuminuria and finally in patients with heart failure and preserved left ventricular function.

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APPENDIX: POTENTIAL CONFLICT OF INTEREST

MV has given lectures for industries producing ARBs.