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Comparative Safety and Tolerability of Angiotensin II Receptor Antagonists

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Abstract

Hypertension is a very common disease and represents a major risk factor for cardiovascular adverse events such as stroke and heart failure. In recent years, a big effort has been put into detecting and treating patients with hypertension. Several classes of drugs acting by different pharmacological mechanisms can be chosen for the treatment of hypertension. However, the long term use of all antihypertensive agents is sometimes limited by the occurrence of adverse effects. Thanks to continuous pharmacological research, new compounds are regularly developed and become available in clinical practice.

Recently, several new, nonpeptide, orally active angiotensin II receptor antagonists have reached the market. Today, these substances represent the most specific way to block the renin angiotensin system. Numerous studies have now demonstrated that these angiotensin II antagonists are as effective as ACE inhibitors, calcium antagonists, β-blockers or diuretics in lowering blood pressure in patients with hypertension.

Given the increasing use of angiotensin II receptor antagonists in the treatment of hypertension, it is important to review their safety and tolerability. Based on the actual level of knowledge, the striking feature of this class of agents is their favourable safety and tolerability profile which appears to be equivalent to that

observed with placebo. Indeed, so far, no clear class-specific adverse effect has been attributed to the angiotensin II receptor antagonists. Thus, if angiotensin II antagonists prevent target organ damage and reduce the morbidity and mortality of patients with hypertension, they may well become a first-line treatment of hypertension.

The pharmacological treatment of hypertension has been shown to drastically reduce the risk of developing cardiovascular diseases such as stroke and congestive heart failure.[1] Therefore, a major effort is being put in detecting and treating patients with hypertension. Today, numerous classes of antihypertensive agents are available to clinicians worldwide: diuretics, β-blockers, calcium antagonists, α_1-adrenoceptor blockers, centrally acting drugs, pure vasodilators and ACE inhibitors.[2] For many years, the optimal treatment of hypertension has been limited by the frequent adverse effects of antihypertensive agents. It is for this reason that pharmacological research has focused on the development of new compounds that have a more specific mode of action, are efficient in a once daily administration and above all exhibit no, or as few as possible, adverse effects.

In this direction, the development of ACE inhibitors in the 1980s was certainly a success but today, the recent introduction of angiotensin II receptor antagonists which block the renin-angiotensin cascade at the receptor level, is undoubtedly a new step forward.[3-6] The higher specificity of these antagonists in blocking the renin-angiotensin system, as compared with ACE inhibitors, was expected to show equal antihypertensive efficacy with a reduced incidence of adverse effects. Losartan potassium was the first nonpeptide angiotensin II antagonist to reach the market and the most clinical experience has been accumulated with this compound. Now, other antagonists such as valsartan, irbesartan, candesartan or eprosartan are available clinically in some countries.

Given the increasingly widespread use of angiotensin II receptor antagonists in the treatment of hypertension, the aim of the present work is to review the safety and tolerability profile of these compounds based on the actual level of knowledge.

1. Safety and Tolerability of Angiotensin II Receptor Antagonists in Clinical Trials

To date, information on the safety and tolerability of the various angiotensin II receptor antagonists are available for several thousands of patients with hypertension included in the numerous clinical studies evaluating the antihypertensive efficacy of angiotensin II antagonists. As mentioned earlier, the greatest bulk of experience has been acquired with losartan potassium which has now been administered to a very large population of patients with hypertension.

1.1 Overall Incidence of Adverse Effects and Withdrawal from Studies

From published clinical trials conducted worldwide, it appears that the main characteristic of angiotensin II antagonists is their favourable adverse effect profile which is comparable with placebo. Thus, with losartan potassium, the overall incidence of any reported clinical adverse events was 15.3% in angiotensin II antagonist–treated patients and 15.5% in the placebo-treated patients.[7] These events were of course not necessarily linked to either losartan potassium or placebo. Comparable figures were obtained with candesartan, valsartan and irbesartan.[8-10] None of the compounds induced a clear, specific, dose-dependent adverse effect that could be attributed to the drug.

With losartan potassium, 2.3% of more than 2000 patients discontinued their treatment because of possible adverse effects as compared with 3.7% who stopped placebo and 2.5 to 9.3% who discontinued other antihypertensive drugs.[11] With candesartan, the withdrawal rate due to adverse events was 2.4 *vs* 2.6% in the placebo group.[8] With irbesartan, 3.3% of patients discontinued therapy be-

cause of adverse events compared with 4.5% of placebo recipients.[10]

1.2 Clinical Adverse Events

1.2.1 Headache, Fatigue and Dizziness

Adverse effects were not frequent in losartan potassium–treated patients and they were similar to those seen in patients treated with placebo. The most frequent drug-related adverse effects were dizziness (2.4%), headache (14.1%), and asthenia/fatigue (2%).[7,12] However, only dizziness occurred with a frequency greater than that observed in placebo treated patients (2.4 *vs* 1.3%) but still lower than that observed with other antihypertensive drugs. With candesartan, valsartan and irbesartan, headache was also a commonly reported adverse effect.[8-10] However, this event was always more frequent in placebo recipients. In addition, with all compounds the incidence of headache decreased with higher dosages of the antagonist. These results would suggest that headache is perhaps a more common symptom of hypertension than believed in patients with mild to moderate hypertension and that effective lowering of blood pressure could effectively reduce the incidence of headache.

1.2.2 Cutaneous Reactions

The incidence of rash in patients undergoing treatment with angiotensin II receptor antagonists was less than what observed in patients treated with placebo. Among the patients who developed cutaneous reactions there was only 1 report of a rash in a patient who was followed-up by a positive rechallenge with losartan potassium.[13]

Another report describes the onset of a Henoch-Schönlein purpura in a patient treated with losartan potassium.[14] Purpura disappeared upon discontinuation of the treatment and rapidly reappeared when losartan potassium was reintroduced.

Two patients have been reported who developed an atypical cutaneous lymphoid hyperplasia while receiving losartan potassium.[15] The skin disorder disappeared upon drug withdrawal. Drug hypersensitivity reactions may induce atypical lymphoid hyperplasia, a phenomenon already observed with ACE inhibitors.[16]

1.2.3 Cough

Cough is an adverse effect that was extensively studied since it is one of the major complaints in patients treated with ACE inhibitors. Cough is considered a class effect of ACE inhibitors linked to the nonspecificity of the angiotensin converting enzyme.[17] Because angiotensin II receptor antagonists do not interfere with the metabolism of kinins and other peptides such as substance P, the absence of cough should represent one of the major clinical advantages of angiotensin II receptor antagonists.

The clinical data show that indeed cough is not an adverse effect of angiotensin II antagonists. Losartan potassium caused a low level of spontaneous reports of cough in patients with hypertension (ranging from 2.3 to 4.1%). Patients receiving ACE inhibitors experienced cough more often (8.8%).[18] In the sole available comparative study, cough was more frequent in patients treated with enalapril than with irbesartan (17 *vs* 10%) but the difference was not statistically different. The incidence of cough in candesartan and valsartan-treated patients was also not different from placebo.[19,20]

Two double-blind studies have addressed specifically the issue of cough with patients complaining of cough while receiving ACE inhibitors. In the first trial, after a positive challenge with lisinopril, patients were randomised into 1 of 3 parallel groups to receive lisinopril, losartan potassium or hydrochlorothiazide.[21] After 8 weeks of treatment, the incidence of cough was comparable in the losartan potassium and the hydrochlorothiazide groups but significantly lower than in the lisinopril group (fig. 1). A similar study design was used to demonstrate that the occurrence of cough under valsartan is comparable to that observed under diuretic therapy but significantly lower than that observed under lisinopril.[22]

1.2.4 Angioedema

Angioedema is another adverse effect related to the use of ACE inhibitors. The development of this

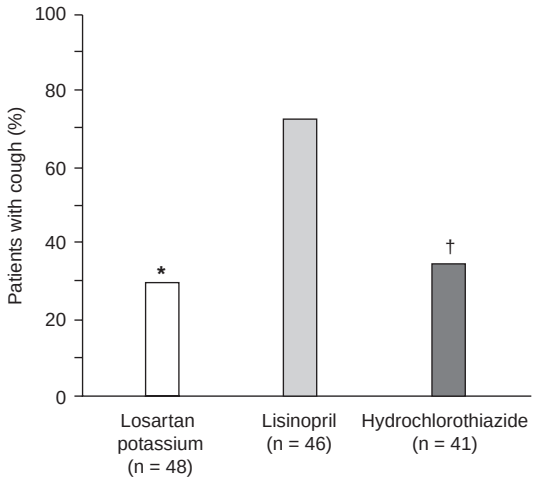

Fig. 1. Percentage of patients with a history of ACE inhibitor–induced cough developing cough after administration of losartan potassium 50 mg/day, lisinopril 20 mg/day, or hydrochlorothiazide 25 mg/day for 8 weeks. * $p < 0.01$ *vs* lisonopril; † $p < 0.05$ *vs* lisonopril.[21]

adverse effect appears to involve the accumulation of bradykinin, but whether this is the unique mechanism remains to be demonstrated.[17,23,24] To date, the data available do not allow to conclude firmly that angiotensin II receptor antagonists cause angioedema. Indeed, there are several reports of angioedema during losartan potassium therapy in the literature[25-27] and it is possible that other cases have occurred but they have not been reported or published. Because angioedema can occur with many substances including drugs and some foods, whether these episodes truly represent a losartan potassium–induced adverse effect is difficult to ascertain.

1.2.5 Other Adverse Effects

Ageusia is a rare complication of ACE inhibitors which has been reported when higher doses of ACE inhibitors were used.[28] Two reports describe cases of patients with progressive dys- or ageusia under treatment with losartan potassium that were reversed after drug withdrawal.[29-30]

One report described migraine in a patient without a history of migraine. Symptoms developed after losartan potassium administration and were confirmed on rechallenge.[31] Another report describes a patient who developed reversible psychosis while receiving losartan potassium therapy, a reaction that completely reversed after drug discontinuation.[32]

1.3 Laboratory Adverse Events

1.3.1 Effect on Haematological Parameters

No consistent, significant adverse effects on routine haematological parameters were noted with the use of losartan potassium,[33] valsartan, irbesartan and candesartan. In the hypertensive population, only minor, clinically nonsignificant decreases of serum haemoglobin levels (1 to 2%) have been reported. However, 1 recent report describes anaemia in patients receiving dialysis who were treated with losartan potassium.[34] There have not been, to date, reported cases of leucopenia or thrombopenia. In post-transplant erythrocytosis, ACE inhibitors have been shown to suppress erythropoiesis. Several case reports and studies in renal transplant patients have suggested that losartan potassium can also lower haematocrit effectively in this situation.[35-39] These results would indicate that the effect of angiotensin II to stimulate erythrocytosis in post-transplant patients is due to the stimulation of angiotensin II AT_1 receptors.

1.3.2 Effect on Potassium Level

Long term treatment with losartan potassium was associated with slight increases in serum potassium levels.[40] This effect is expected and is linked to the transient decrease in plasma aldosterone levels. However, this increase did not lead to discontinuation of the antihypertensive treatment. In patients with hypertension with a normal renal function, the changes in serum potassium level induced by valsartan, candesartan cilexetil and irbesartan were negligible. With losartan potassium, the incidence of hyperkalaemia (1.5%) was similar to that observed with ACE inhibitors (1.3%) and placebo. As for ACE inhibitors, hyperkalaemia is more likely to develop in patients with renal insufficiency, or with diabetes mellitus, or in those patients taking potassium-sparing diuretics or potassium supplementation.

1.3.3 Effect on Liver Enzyme Levels

Elevation of transaminase levels (2 to 3 times above the baseline level) occurred rarely and usually resolved with or without discontinuation of losartan potassium therapy.[40] In only 1 patient was it necessary to discontinue the losartan potassium treatment.[25] Among patients treated with candesartan cilexetil, occasional minor increases in plasma liver enzymes levels (particularly ALT) have been observed which were usually transient despite continued therapy. No other change consistent with an effect on the liver was found. More frequent alterations of plasma liver enzymes levels have been reported with the long-acting angiotensin II antagonist tasosartan and have lead to the withdrawal of the drug. Thus, whether the elevation of transaminase levels represents a class effect or a specific adverse effect of tasosartan is not really clear today.

1.3.4 Effect on Uric Acid Excretion

Losartan potassium has been shown to increase urinary uric acid excretion and hence to lower plasma uric acid in individuals who are normotensive.[41,42] The uricosuric effect of losartan potassium is due to a specific effect of losartan potassium on urate transport in the renal proximal tubule and is independent of angiotensin II receptor blockade.[43] EXP3174, the active metabolite of losartan potassium has no effect on uric acid excretion.[44] A decrease in serum uric acid levels has been found consistently in patients with hypertension treated with losartan potassium. In diuretic-treated patients, the addition of losartan potassium has been shown to prevent the diuretic-induced increase in serum uric acid level.[45] The uricosuric effect of losartan potassium is not associated with an increased incidence of urate stone formation. This may be due to the fact that losartan potassium simultaneously increases urinary pH by decreasing the proximal reabsorption of bicarbonate.[42,46]

In cyclosporin-treated hyperuricaemic heart transplant patients, losartan potassium has also been shown to reduce serum uric acid levels.[47] As with other hypouricaemic agents, the losartan potassium-induced decrease in uric acid may occasionally trigger an episode of gout.[47] The other nonpeptide angiotensin II antagonists have no effect on uric acid excretion.[48,49]

1.3.5 Other Adverse Effects

Angiotensin II receptor antagonists did not show any effect on serum cholesterol or plasma lipoprotein levels.[50] A preliminary study suggests that losartan potassium may improve the lipid profile of patients with nephrotic syndrome.[51] This effect on plasma lipids may be linked to the ability of losartan potassium to lower proteinuria. No adverse effect of angiotensin II receptor antagonists was observed on serum glucose levels and preliminary studies suggest that losartan potassium has a neutral effect on insulin sensitivity and glucose and lipid metabolism.[52,53]

ACE inhibitors are also a rare cause of pancreatic inflammation.[54] Recently, 2 case of pancreatitis in patients receiving losartan potassium were published.[55,56]

1.4 First Dose Hypotension and Rebound Hypertension

First dose hypotension is a common problem when ACE inhibitors are administered to salt-depleted or hypovolaemic patients with hypertension. Indeed, in these conditions blood pressure maintenance depends very much on the renin-angiotensin system. Thus, analysis of adverse effects which could suggest the occurrence of a first-dose hypotension have been undertaken in patients treated with angiotensin II receptor antagonists. In diuretic-treated patients, the addition of increasing doses of losartan potassium did not cause first-dose hypotension.[40,45] In another study, the occurrence of orthostatic hypotension did not differ in candesartan- and placebo-treated patients with hypertension.[57] Even in elderly patients who are more susceptible to first-dose hypotension, candesartan cilexetil did not produce orthostatic hypotension.[58]

Rebound hypertension may be a problem with drugs acting directly on a receptor. Indeed, plasma angiotensin II levels increase significantly during angiotensin II receptor blockade.[59] Thus, acute

withdrawal of therapy could at least theoretically lead to a sudden increase in blood pressure. Studies conducted with losartan potassium and irbesartan cilexetil have demonstrated that rebound hypertension is not a problem with angiotensin II receptor antagonists.[40,57,60,61]

2. Safety and Tolerability in Special Populations

The safety and tolerability of angiotensin II receptor antagonists as well as their efficacy were carefully evaluated as a function of patients' gender, age and race. None of these factors were found to influence the incidence of adverse effects. In particular, angiotensin II receptors antagonists are equally well tolerated by elderly (>65 years), younger (<65 years) and very old patients (>75 years).[57,58,62-64]

2.1 Patients with Renal Impairment

The clearance of losartan potassium is primarily nonrenal whereas the clearance of the active metabolite EXP3174 occurs through both renal and nonrenal routes.[65] Irbesartan undergoes no significant renal clearance (<5%) whereas there renal contribution to the systemic clearance of valsartan and candesartan is 30 and 60%, respectively.[64,66,67] In the general population of patients with mild to moderate hypertension included in the clinical trials, adverse effect on renal function parameters were not found with any of these antagonists.[57,63-65,68]

The tolerability of losartan potassium has been examined in 112 patients with hypertension and chronic renal insufficiency ranging from mild renal failure to the need for haemodialysis.[69] Losartan potassium was well tolerated in all groups of patients. No significant change in creatinine clearance was observed during the 12 weeks of administration. The changes in serum potassium levels were only minor and not significant. An increase in potassium level greater than 0.5 mmol/L from baseline was observed in 8 to 18% of the patients depending on the severity of renal insufficiency and treatment in 1 patient was discontinued because of hyperkalaemia.[69] No significant change in haemoglobin level was found.

In patients with hypertension with or without renal diseases, angiotensin II receptor antagonists increase renal plasma flow, decrease renal resistances and have no significant effect on glomerular filtration rate.[70,71]

In patients with renal artery stenosis, mainly when it is bilateral or occurring in a single functioning kidney, blockade of the renin-angiotensin system may cause a deterioration of renal function. So far, few studies have evaluated the safety of angiotensin II receptor antagonists in patients with renal artery stenosis. In a preliminary report, renal haemodynamics were measured in 17 patients with atheromatous renal artery stenosis and mild to moderate renal failure receiving a single dose of losartan potassium 200mg and captopril 50mg. In this small study, both losartan potassium and captopril had a deleterious effect on renal haemodynamics, a transient anuria occurring after both agents in 1 patient with bilateral renal artery stenosis.[72] Another report describes an alteration of renal function parameters in a woman treated with losartan potassium.[73] Of note, the patient had diabetes mellitus and had a history of diffuse vascular disease and therefore was at risk of developing renal dysfunction. Taken together, these preliminary results suggest that, as with ACE inhibitors, acute renal failure may occur with angiotensin II receptor antagonists when administered to patients with severe renal artery stenosis or diffuse intrarenal vascular sclerosis.

2.2 Patients with Hepatic Impairment

Although most angiotensin II receptor antagonists are partly cleared by the liver and bile, few studies have examined the safety and tolerability of these agents in patients with hepatic impairment. Several studies have shown that the pharmacokinetics of losartan potassium, valsartan and candesartan are not significantly altered in patients with mild to moderate liver dysfunction.[67,68,74,75]

2.3 Patients with Congestive Heart Failure

Blockade of the renin-angiotensin system is a well accepted approach to the treatment of congestive heart failure. Angiotensin II receptor blockade might also be advantageous in this indication. Several preliminary studies have indeed demonstrated that angiotensin II receptor antagonists have favourable haemodynamic effects in heart failure.[76-78]

The Evaluation of Losartan in the Elderly (ELITE) study[79] was designed to compare the safety and tolerability of losartan potassium and captopril in elderly patients with heart failure. In addition, the incidence of renal dysfunction, hypotension-related symptoms, hyperkalaemia and cough were analysed. In this study, involving 722 patients, a persistent increase in serum creatinine level (>0.3 mg/dl) was observed in 10.5% of losartan potassium–treated patients and 10.5% of those receiving captopril. The incidence of cough was significantly lower in the losartan potassium group (6.5% *vs* 17.8%, $p < 0.001$). Persistent increases in serum potassium level (≥0.5 mEq/L) were found in 18.8% of the patients treated with losartan potassium and 22.7% of those treated with captopril ($p = 0.069$). Significantly fewer treatment discontinuations were observed in the losartan potassium group (43 *vs* 77 in the placebo group, $p < 0.002$). These data therefore suggest that angiotensin II receptor antagonists are well tolerated in heart failure.

2.4 Safety in Pregnancy and Fetal Toxicity

The administration of ACE inhibitors during pregnancy can lead to severe hypotension and renal failure in the newborn.[80] Hence, ACE inhibitors should not be administered to women who are pregnant. Developmental and fetal toxicology studies suggest that angiotensin II receptor antagonists should also be discontinued during pregnancy. Losartan potassium administered to animals had no effect on fetal development in the first trimester; however, when it was administered in the second and third trimesters, it was associated with serious fetal toxicity.

It is unknown whether angiotensin II receptor antagonists are excreted in human breast milk. However, in rats, losartan potassium and its active metabolite were detected in milk. Therefore, the risk of using angiotensin II receptor antagonists in breast-feeding mothers should be taken into account.

3. Drug Interactions

Data from pharmacokinetic or pharmacodynamic interaction studies showed that angiotensin II receptor antagonists had no clinically important interactions with other agents commonly used in patients with hypertension. As expected, salt depletion and concomitant use of thiazide diuretics have been shown to potentiate the hypotensive effect of angiotensin II receptor antagonists. Published data on drug interactions show that angiotensin II receptor antagonists can be safely given with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (phenobarbitone) and ketoconazole.[63,64,81]

A study conducted in normotensive individuals suggests that the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) abolishes the natriuretic response to angiotensin II receptor blockade.[82] Hence, the concomitant use of NSAIDs may potentially blunt the antihypertensive efficacy of angiotensin II receptor antagonists as they do with ACE inhibitors or diuretics.

4. Comparative Safety and Tolerability Among Different Antihypertensive Agents

A comparison of the safety and tolerability of different antihypertensive regimens with angiotensin II receptor antagonists is presented in table I. When compared with ACE inhibitors, angiotensin II antagonists do not cause cough. The use of calcium antagonists is frequently accompanied by leg oedema (14%) and flushes, adverse effects which do not occur with angiotensin II receptor antagonists. The incidence of oedema with angiotensin II receptor antagonists is the same as with placebo (1.7%). Insomnia and headache appear more often

when β-blockers are used (4.4 and 19.1%) than when angiotensin II antagonists are administered (1.1 and 14.1%). Dyspnoea and cold extremities occur with β-blockers but have not been reported with angiotensin II receptor antagonists. The use of diuretics is frequently associated with asthenia/fatigue (5.5%), gout and impotence. With angiotensin II receptor antagonists the incidence of asthenia/fatigue was low (3.8%) and whether gout episodes may occur with losartan potassium has not been confirmed so far.

5. Unopposed Angiotensin II AT_2 Receptor Stimulation

The blockade of angiotensin II AT_1 receptors with a specific antagonist results in an increase in plasma angiotensin II levels[59] which can stimulate unblocked AT_2 receptors. So far, the clinical role of AT_2 receptors remains largely unknown. Experimentally, AT_2 receptors may play a role in mediating apoptosis and cell differentiation in adult or tumour tissues and may contribute to the long term growth response to angiotensin II.[83] Antiproliferative effects have also been linked to AT_2 receptors.[84] At the present time, it is unclear whether the unopposed effects of angiotensin II on other binding sites are of any clinical significance to the safety profile and cardiovascular effects of angiotensin II receptor antagonists. So far, the clinical experience accumulated with the various antagonists has not produced any serious concern but the clinical follow-up may still be too short to draw firm conclusions.

6. Conclusions

Data from published studies show that angiotensin II receptor antagonists are effective antihypertensive agents with an excellent safety and tolerability profile. When compared with ACE inhibitors, β-blockers, diuretics or calcium antagonists, these compounds seem to be free of those adverse effects that limit compliance, including cough, because of their high specificity for the angiotensin II AT_1 receptor. The most frequent clinical adverse event reported was dizziness. The occurrence of adverse effects was not accentuated with age and was affected neither by gender nor by race.

Angiotensin II receptor antagonists do not interfere with other cardiovascular risk factors as they are neutral on glucose and lipid metabolism. Preliminary studies suggest that angiotensin II antagonists like ACE inhibitors have a favourable impact on renal function. In patients with hypertension

Table I. Adverse effect profiles of the different classes of antihypertensive drugs

Adverse effect	Angiotensin II receptor antagonists	ACE inhibitors	Diuretics	β-Blockers	Calcium antagonists
Headache	–	–	–	–	+
Flush	–	–	–	–	+[a]
Oedema	–	–	–	–	+
Dyspnoea	–	–	–	+	–
Bradycardia/arrythmia	–	–	–	+	+[b]
Fatigue	–	–	±	+	–
Cold extremities	–	–	–	+	–
Impotence	–	–	+	+	–
Gout	–	–	+	–	–
Cough	–	+	–	–	–
Orthostatic hypotension	–	–	+	–	–

a Mainly with dihydropyridines.

b Occurring mainly with diltiazem and verapamil.

+ indicates adverse effect associated with the drug class; **–** indicates adverse effect not associated with the drug class; ± indicates adverse effect may be associated with the drug class.

and renal insufficiency or severe heart failure, angiotensin II receptor blockade may cause hyperkalaemia. As observed with ACE inhibitors, acute renal failure may occur in patients with bilateral renal artery stenosis or a stenosis of a solitary kidney.

Because of their excellent safety and tolerability profile, angiotensin II receptor antagonists represent a good alternative for the treatment of hypertension. Several large trials are now underway to demonstrate that these agents are not only effective in lowering blood pressure but also in preventing target organ damage and hence reducing cardiovascular morbidity and mortality. If this is the case, angiotensin II receptor antagonists will certainly become one of the first-line treatments for hypertension.

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