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## Angiotensin II Type 1 Receptor Blockers

Michel Burnier, MD

In the 1970s, a series of observations demonstrated that Angiotensin II has deleterious effects on the heart and kidney and that patients with high levels of plasma renin activity are at a higher risk of developing stroke or myocardial infarction than those with low plasma renin activity.<sup>1,2</sup> Thereafter, the development of pharmacological probes that block the renin-angiotensin system helped define the contribution of this system to blood pressure control and to the pathogenesis of diseases such as hypertension, congestive heart failure, and chronic renal failure. Thus, the concept of treating hypertension and congestive heart failure by a specific blockade of the renin-angiotensin system was first established with the use of saralasin, a nonselective peptidic antagonist of angiotensin II receptors.<sup>3-9</sup> With saralasin, it became possible to demonstrate that angiotensin II receptor blockade, alone or in combination with salt depletion, lowers blood pressure in hypertensive patients and improves systemic hemodynamics in patients with congestive heart failure.<sup>3-10</sup> However, saralasin had many drawbacks. Because it is a peptide, it had to be administered intravenously. This characteristic limited its use to hours or a few days at maximum. In addition, at higher doses, saralasin had some partial agonist, angiotensin II-like effects.

The next major breakthrough in the understanding of the renin-angiotensin system was triggered by the development of orally active angiotensin-converting enzyme (ACE) inhibitors.<sup>10-15</sup> Studies performed with these agents rapidly confirmed and reinforced the seminal clinical observations made with saralasin. ACE inhibitors are now recognized as an important therapeutic step to control blood pressure in hypertensive patients and to reduce morbidity and mortality in patients with congestive heart failure.<sup>16</sup> In addition, because of their ability to lower proteinuria, ACE inhibitors have become an essential component of the treatment of chronic renal diseases to delay the progression of renal failure.<sup>17</sup> ACE inhibitors are also very effective in reducing cardiovascular morbidity and mortality in patients with a high cardiovascular risk profile, including diabetics.<sup>18</sup>

ACE is an enzyme with multiple effects, not all of which are mediated through angiotensin receptors. Thus, the hope has been that angiotensin II receptor blockers would produce more specific actions and fewer side effects than ACE inhibitors. When ACE inhibitors became available, the more specific approach of blocking angiotensin II receptors was

abandoned. Nevertheless, research continued. This resulted in the most recent therapeutic development of specific, nonpeptide, orally active angiotensin II receptor antagonists.<sup>19</sup>

### The Renin-Angiotensin Cascade and Angiotensin II Receptor Subtypes

The renin-angiotensin system is an enzymatic cascade that starts with the cleavage of angiotensinogen by renin to form the inactive decapeptide angiotensin I. Thereafter, angiotensin I is converted by ACE to form angiotensin II. Although there are other angiotensin peptides with biological effects, angiotensin II is the major end product of the system. However, angiotensins I and II can be generated by other enzymatic pathways.<sup>20,21</sup> Thus, angiotensin I can be formed by nonrenin enzymes such as tonin or cathepsin, and angiotensin I can be converted to angiotensin II by enzymes such as trypsin, cathepsin, or the heart chymase. Today, the quantitative contribution of these alternative pathways to the generation of angiotensin II remains unclear.

ACE is also called kininase II, and it participates in metabolizing bradykinin to inactive peptides. The inhibition of ACE produces an increase in plasma bradykinin levels.<sup>22,23</sup> This increase surely contributes to the side effects of ACE inhibitors (eg, angioedema) and may play a role in the organ-specific effects of ACE inhibitors.<sup>23</sup> Whether bradykinin accumulation contributes to the antihypertensive efficacy of ACE inhibitors is less clear, despite some findings in experimental models of hypertension<sup>22,24-26</sup> and some clinical results suggesting that bradykinin plays a role in the short-term blood pressure lowering effect of ACE inhibition in humans.<sup>27,28</sup>

The discovery of specific angiotensin II receptor antagonists has confirmed the existence of various subtypes of angiotensin II receptors.<sup>19</sup> Angiotensin II type 1 (AT<sub>1</sub>) receptors are selectively inhibited by losartan and are sensitive to dithiothreitol, whereas type 2 (AT<sub>2</sub>) receptors are inhibited by PD 123177 and related compounds but are insensitive to dithiothreitol. In rodents, AT<sub>1</sub> receptors have been further subdivided into AT<sub>1A</sub> and AT<sub>1B</sub>. In amphibians and in neuroblastoma cell lines, an angiotensin II receptor inhibited neither by losartan nor by PD 123177 has been classified as AT<sub>3</sub>. Both the AT<sub>1</sub> and the AT<sub>2</sub> receptors have been cloned.<sup>29-31</sup> They belong to the superfamily of G-protein-coupled receptors that contain 7 transmembrane regions.

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**TABLE 1. Angiotensin II Receptors and Their Functions and Location**

Receptor	Actions	Location
AT <sub>1</sub>	Vasoconstriction, increase sodium retention, suppress renin secretion, increase endothelin secretion, increase vasopressin release, activate sympathetic activity, promote myocyte hypertrophy, stimulate vascular and cardiac fibrosis, increase myocardial contractility, induce arrhythmias, stimulate plasminogen activator inhibitor 1, and stimulate superoxide formation	Vessels, brain, heart, kidney, adrenal gland, and nerves
AT <sub>2</sub>	Antiproliferation/inhibition of cell growth, cell differentiation, tissue repair, apoptosis, vasodilation (NO mediated?), kidney and urinary tract development, control of pressure/natriuresis, stimulate renal prostaglandins, and stimulate renal bradykinin and NO	Adrenal gland, heart, brain, myometrium, fetus, and injured tissues
AT <sub>3</sub>	Unknown	Neuroblastoma cells in amphibians
AT <sub>4</sub>	Renal vasodilator; stimulate plasminogen activator inhibitor 1	Brain, heart, vessels, lungs, prostate, adrenal gland, and kidney

Their amino acid sequence seems to be highly conserved across species and across tissues within a species. AT<sub>1</sub> and AT<sub>2</sub> receptors share only ≈34% homology and have distinct signal transduction pathways.

AT<sub>1</sub> receptors have been localized in the kidney, heart, vascular smooth muscle cells, brain, adrenal gland, platelets, adipocytes, and placenta. AT<sub>2</sub> receptors are abundant in the fetus, but their number decreases in the postnatal period.<sup>19</sup> In adult tissues, AT<sub>2</sub> receptors are present only at low levels, mainly in the uterus, the adrenal gland, the central nervous system, the heart (cardiomyocytes and fibroblasts), and the kidney.<sup>19</sup> AT<sub>2</sub> receptors seem to be re-expressed or upregulated in experimental cardiac hypertrophy, myocardial infarction, and vascular and wound healing.<sup>32–34</sup>

As shown in Table 1, all the known clinical effects of angiotensin II are mediated by the AT<sub>1</sub> receptor. The physiological role of AT<sub>1</sub> receptors is very well documented experimentally and clinically. AT<sub>1A</sub> receptor knockout mice are characterized by a low blood pressure and high circulating renin levels.<sup>35</sup> These mice were also recently shown to display less left ventricular remodeling and an improved survival after myocardial infarction.<sup>36</sup> The physiological role of the AT<sub>2</sub> receptor is only partially understood. In recent years, several new functions have been attributed to AT<sub>2</sub> receptors, including inhibition of cell growth, promotion of cell differentiation, and apoptosis.<sup>37–40</sup> Thus, AT<sub>2</sub> receptors could have an important role in counterbalancing some of the effects of angiotensin II mediated by AT<sub>1</sub> receptors. However, this topic remains a matter of debate because contro-

versial results have been published.<sup>41,42</sup> More recent data also suggest that AT<sub>2</sub> receptors could mediate the production of bradykinin, nitric oxide, and perhaps prostaglandins in the kidney.<sup>43</sup> Additional studies are now needed to confirm these multiple roles of AT<sub>2</sub> receptors in humans.

### Pharmacology of AT<sub>1</sub> Receptor Blockers

In recent years, numerous orally active, selective AT<sub>1</sub> receptor antagonists have been synthesized.<sup>44</sup> Today 6 of them have been accepted by the US Food and Drug Administration and can be used in the United States and various European countries for the treatment of hypertension. Other compounds may be launched in the future. As shown in Table 2, these antagonists share some pharmacological characteristics. First, they have a high affinity for AT<sub>1</sub> receptors (in the low nanomolar range) and almost no affinity for AT<sub>2</sub> receptors. Second, all antagonists display very high protein binding. Finally, when studied *in vitro*, most (if not all) AT<sub>1</sub> receptor antagonists induce, to a variable degree, an “insurmountable blockade.” This behavior describes the nonparallel displacement of the angiotensin II response curves seen during *in vitro* studies. Surmountable/insurmountable antagonism describes the interaction with the antagonist after a preincubation step, whereas competitive/noncompetitive antagonism is related to experimental conditions in which ligand and antagonist are added simultaneously. Studies have convincingly demonstrated that all AT<sub>1</sub> receptor antagonists are competitive, with a very slow dissociation from the receptor.<sup>45,46</sup> Because insurmountable blockade is difficult to

**TABLE 2. Pharmacokinetic Properties of Angiotensin II Receptor Antagonists**

Drug (Active Metabolite)	AT <sub>1</sub> Receptor Affinity, nmol/L	Bioavailability, %	Food Effect	Active Metabolite	Half-Life, h	Protein Binding, %	Dosage, mg/d
Losartan (EXP 3174)	IC <sub>50</sub> , 20	33	No	Yes	2 (6–9)	98.7 (99.8)	50–100
Valsartan	IC <sub>50</sub> , 2.7	25	Yes, –40%	No	9	95	80–320
Irbesartan	IC <sub>50</sub> , 1.3	70	No	No	11–15	90*	150–300
Candesartan cilexetil (TCV 116)	...	...	No	Yes	3.5–4	...	4–16 (32)
(CV11974)	K <sub>i</sub> , 0.6	42			3–11	99.5	
Telmisartan	K <sub>i</sub> , 3.7	43	No	No	24	>99	40–80
Eprosartan	IC <sub>50</sub> , 1.4–3.9	15	No†	No	5–7	98	400–800

Values are mean or range. K<sub>i</sub> indicates inhibition constant.

\*Some studies suggest that irbesartan has a greater protein binding (>95%).

†Depending on the formulation, there may be a food effect.

achieve at the doses used clinically, it will not be discussed in more detail. Studies performed in normotensive subjects have demonstrated consistently that AT<sub>1</sub> receptor antagonists dose-dependently block the pressor response to exogenous angiotensin II.<sup>47-50</sup>

### Losartan

Losartan was the first orally active AT<sub>1</sub> receptor antagonist available on the market, and it is the antagonist with which the greatest clinical experience has been accumulated. It represents the prototype of a highly selective AT<sub>1</sub> receptor antagonist and was derived from the Takeda series of 1-benzylimidazole-5-acetic acid derivatives recognized to be weak angiotensin II antagonists.<sup>19</sup> In vitro, losartan competes with the binding of angiotensin II to AT<sub>1</sub> receptors; the concentration that inhibits 50% of the binding of angiotensin II (IC<sub>50</sub>) is 20 nmol/L. Losartan has a major active metabolite, EXP 3174. Administered intravenously, EXP3174 is 10 to 20 times more potent than losartan and has a longer duration of action than losartan. However, the oral bioavailability of EXP 3174 is very low. Thus, the drug on the market is losartan, but most of losartan's effect is due to EXP 3174. The main pharmacokinetic characteristics of losartan and EXP 3174 are presented in Table 2. Losartan and its metabolite are excreted by the kidney and in bile. Neither compound is dialysed.

### Valsartan

Valsartan is a nonheterocyclic antagonist in which the imidazole of losartan has been replaced with an acylated amino acid. It is also a potent AT<sub>1</sub> antagonist (IC<sub>50</sub> of 2.7 nmol/L on rat aorta). Valsartan does not need to be metabolized to be effective, and it is excreted both by the bile (70%) and the kidneys (30%). There is only one inactive metabolite. Food decreases drug absorption by ≈40%. Like losartan, valsartan lacks affinity for adrenergic, histamine, substance P, muscarinic, and serotonin receptors.

### Irbesartan

Irbesartan is a longer acting AT<sub>1</sub> receptor antagonist than losartan and valsartan (Table 2). It also has a high affinity for the AT<sub>1</sub> receptor (IC<sub>50</sub> of 1.3 nmol/L in rat liver) and no affinity for AT<sub>2</sub> receptors. Structurally, it contains an imidazolinone ring in which a carbonyl group functions as a hydrogen bond acceptor in place of the C5 hydroxymethyl group of losartan. In contrast to losartan, irbesartan has no active metabolite. It is cleared predominantly by the bile (80%) and partly by the kidney (20%). Irbesartan has a large volume of distribution (53 to 93 L versus 12 L for EXP 3174 and 17 L for valsartan). Clinically, irbesartan has been evaluated at doses up to 900 mg/d. Irbesartan induced a dose-related blood pressure response, with a plateau at 300 mg.<sup>51</sup>

### Candesartan Cilexetil

Candesartan is also a long-acting angiotensin II receptor antagonist. To overcome a poor oral absorption, a series of ester prodrugs was synthesized, and candesartan cilexetil was identified as the compound that provided the best angiotensin II antagonistic activity profile after oral administration. Thus,

candesartan cilexetil is a prodrug that is rapidly and completely converted to the active compound candesartan during gastrointestinal absorption. Candesartan AT<sub>1</sub> binding affinity in the rabbit aorta is 80 times greater than that of losartan and 10 times greater than that of EXP 3174, the active metabolite of losartan. In vivo, candesartan has a relatively long half-life (≈9 hours), which seems to be somewhat longer in the elderly (9 to 12 hours). Candesartan is eliminated principally by the kidneys (≈60%) and to a lesser extent through the bile (40%). There is no significant drug accumulation in patients with mild renal impairment. At doses >12 mg/d, an accumulation of candesartan cilexetil may be observed in patients with severe renal dysfunction. The mean extraction ratio for candesartan from dialysed blood is low.

### Telmisartan

Telmisartan is the longest acting angiotensin II AT<sub>1</sub> receptor antagonist currently available. Its mean elimination half-life is ≈24 hours in patients with mild to moderate hypertension who receive 20 to 160 mg/d telmisartan for 4 weeks. Telmisartan is directly active; it undergoes minimal transformation and is excreted almost completely by the feces (98%).

### Eprosartan

Eprosartan is the latest angiotensin II receptor antagonist. Eprosartan has the shortest half-life of the 6 antagonists currently available (elimination half-life of 5 to 7 hours), and most of the initial clinical studies have been conducted using a twice a day regimen at doses up to 400 mg BID. In vivo, both biliary (90%) and renal (10%) excretion pathways contribute to the elimination of eprosartan. Depending on the formulation, the absorption of eprosartan may be reduced by 25% and retarded by 1.5 hours when the drug is administered with food.<sup>52</sup> The renal clearance of eprosartan seems to be slowed in subjects with renal insufficiency.<sup>52</sup> However, because only a small fraction of eprosartan is cleared by the kidney, no dose adjustment seems to be necessary in patients with chronic renal failure.

## AT<sub>1</sub> Receptor Blockers in Hypertension

Numerous studies have evaluated the antihypertensive efficacy of angiotensin II receptor antagonists in patients with mild to moderate or severe hypertension.<sup>53-80</sup> In these studies, angiotensin II receptor antagonists have been compared with ACE inhibitors, calcium antagonists, β-blockers, and diuretics.<sup>53-80</sup> The efficacy and tolerability of AT<sub>1</sub> receptor antagonists has also been evaluated in various populations and age groups when administered either alone or in combination with diuretics. Overall, the results of these studies show that the 6 angiotensin II antagonists are as effective as ACE inhibitors, calcium antagonists, β-blockers, and diuretics. In monotherapy, angiotensin II antagonists induce a similar decrease in blood pressure in young and elderly patients and in men and women. Administered as monotherapy, angiotensin II antagonists, like ACE inhibitors, are less effective in reducing blood pressure in black patients, but this is not the case when angiotensin II antagonists are combined with a diuretic. The antihypertensive efficacy of angiotensin II

receptor antagonists is potentiated by the addition of a small dose of a thiazide diuretic.

### Tolerability of Angiotensin II Receptor Antagonists

Clinically, all angiotensin II receptor antagonists have an excellent tolerability profile, with an incidence of side effects that is not different from placebo.\* They<sup>81</sup> do not produce first-dose hypotension. Because plasma angiotensin II levels increase markedly during angiotensin II receptor blockade, rebound hypertension was initially a matter of concern if drug therapy was withdrawn quickly. No rebound hypertension has been demonstrated on withdrawal of losartan. Unlike ACE inhibitors, angiotensin II receptor antagonists do not produce a cough.<sup>82–84</sup> Some cases of angioedema have been reported with the administration of losartan.<sup>85</sup> However, because angioedema may occur with many substances, including drugs and some food products, it is difficult to ascertain whether these published cases of angioedema are really linked to the administration of the antagonist. Like ACE inhibitors, all angiotensin II receptor antagonists are contraindicated during pregnancy.

Angiotensin II antagonists have no major effect on routine laboratory parameters. Like ACE inhibitors, they have been shown to lower hematocrit in post-transplant erythrocytosis.<sup>86,87</sup> Losartan has been shown to increase urinary uric acid excretion.<sup>88,89</sup> The uricosuric effect of losartan 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.<sup>90</sup> It has not been observed with other angiotensin II blockers. In the Evaluation of Losartan In the Elderly (ELITE) trial, no difference in the incidence of renal dysfunction among elderly patients receiving losartan (50 mg daily) and those treated with the ACE inhibitor captopril (50 mg TID) was found.<sup>91</sup>

Occasionally, minor and transient increases in liver enzyme activity (particularly alanine aminotransferase) have been observed with angiotensin II receptor antagonists.<sup>81</sup> In vivo, telmisartan causes a variable increase in digoxin serum levels. Thus, plasma digoxin levels should be monitored when telmisartan is combined with digoxin. Warfarin levels may also be reduced during coadministration with telmisartan.

### Angiotensin II Receptor Antagonists in Renal and Congestive Heart Failure

In experimental and small clinical studies, angiotensin II receptor antagonists had renal effects similar to ACE inhibitors. Thus, angiotensin II receptor antagonists seem to have no influence on glomerular filtration rate and to increase renal blood flow; hence, the filtration fraction decreases.<sup>89,92–94</sup> Angiotensin II antagonists induce also a natriuretic response that may contribute to their antihypertensive efficacy.<sup>89,92</sup> Preliminary experimental and clinical studies obtained with the angiotensin II receptor antagonists on small groups of patients suggest that these agents can decrease the filtration fraction and reduce urinary albumin excretion.<sup>93,95–99</sup> This

may suggest a favorable influence on renal function in patients with chronic renal failure. Finally, preliminary results suggest that, as with ACE inhibitors, acute renal failure may occur with angiotensin II antagonists when administered to patients with renal artery stenosis or diffuse intrarenal vascular stenosis.<sup>81</sup>

Because the use of ACE inhibitors is a recommended approach for the management of patients with heart failure and an effective treatment to induce the regression of left ventricular hypertrophy in hypertensive patients, several studies have investigated the effect of angiotensin II receptor blockade in these clinical indications. Thus, a recent study has demonstrated that valsartan produces a significant regression of left ventricular hypertrophy in previously untreated patients with essential hypertension.<sup>100</sup> In heart failure, several short-term studies indicate that AT<sub>1</sub> receptor antagonists have beneficial, systemic hemodynamic effects and are well-tolerated drugs.<sup>101–105</sup> For these indications, preliminary studies have suggested that AT<sub>1</sub> receptor antagonists are at least as efficacious as ACE inhibitors but have a more favorable side-effect profile. In the ELITE trial, one of the secondary end points (ie, combined mortality and hospitalization for heart failure) was surprisingly lower in the losartan group.<sup>91</sup> These positive preliminary results were not confirmed in ELITE II, which involved more patients. Indeed, ELITE II confirmed that patients treated with losartan had significantly fewer side effects than those on captopril, but losartan was not superior to captopril in reducing morbidity and mortality.<sup>106</sup> Nonetheless, although the actual data suggest that angiotensin II receptor blockers have no clear advantage over ACE inhibitors in heart failure, except for their better tolerability, one should be careful before concluding that the class of angiotensin receptor antagonists is less effective than ACE inhibitors in the treatment of congestive heart failure based on the results of ELITE II. Additional studies are ongoing, and their results will have to be taken into account to evaluate the place of angiotensin II receptor antagonists in heart failure.

### Are There Differences Between Angiotensin II Receptor Antagonists?

Angiotensin II receptor antagonists share the same mechanism of action. However, they have different pharmacokinetic profiles, which may account for potential differences in efficacy. In addition, the selected starting dose may have been chosen using different criteria, thus resulting in noncomparable degrees of blockade of the renin-angiotensin system.<sup>107</sup> The relative antihypertensive efficacy of angiotensin II receptor antagonists was evaluated in a recent meta-analysis of 43 randomized, placebo-controlled trials.<sup>108</sup> This comprehensive analysis suggests comparable antihypertensive efficacy within the angiotensin II receptor antagonist class. However, several double-blind, head-to-head comparative studies have evaluated the relative antihypertensive efficacy of some angiotensin II receptor antagonists in patients with mild to moderate hypertension.<sup>109–114</sup> Their results suggest that longer acting angiotensin II antagonists such as irbesartan, candesartan, and telmisartan may be more effective than losartan, particularly at trough, thus providing better 24-hour control of blood pressure. The difference between antagonists

\*References 55–59, 61, 63–68, 71–73, 75, 78, 80, 81.

**TABLE 3. Ongoing Clinical Trials With Angiotensin II Receptor Blockers**

Disease	Drug	Trial	No. of Patients	End Points	Date of Completion/Results
<b>Hypertension</b>					
With left ventricular hypertrophy	Losartan	LIFE	9194	Mortality, MI, stroke	2001
With high cardiovascular risk	Valsartan	VALUE	14 400	Cardiovascular mortality	2004
In elderly	Candesartan	SCOPE	4400	Cardiovascular mortality Stroke, MI	2001
<b>Heart failure</b>					
	Losartan	ELITE II	3121	All-cause mortality, cardiovascular mortality	1999: losartan not superior to captopril but losartan better tolerated than captopril
	Valsartan	Val-HeFT	5200	All-cause mortality	2000: valsartan superior to placebo on combined mortality and morbidity in ACEI and diuretic-treated patients; most benefits in ACEI-intolerant patients
LVEF $\leq$ 0.40	Candesartan	CHARM II	2300	All-cause mortality	2002
LVEF $\leq$ 0.40 and ACEI intolerant	Candesartan	CHARM I	1700	All-cause mortality	2002
With LVEF $>$ 0.40	Candesartan	CHARM III	2500	All-cause mortality	2002
<b>After myocardial infarction</b>					
With left ventricular dysfunction	Losartan	OPTIMAAL	5000	All-cause mortality	2001
With left ventricular dysfunction	Valsartan	VALIANT	14 500	All-cause mortality	2005
<b>Type II diabetes</b>					
	Valsartan	ABCD-2V	800	Mortality, doubling of creatinine, ESRD	2003
With nephropathy	Losartan	RENAAL	1520	Mortality, doubling of creatinine, ESRD	2001
With nephropathy	Irbesartan	IDNT	1650	Mortality, doubling of creatinine, ESRD	2001
In hypertensives	Irbesartan	IRMA II	611	Microalbuminuria	2001

MI indicates myocardial infarction; LVEF, left ventricular ejection fraction; ESRD, end-stage renal disease; LIFE, Losartan Intervention For Endpoint reduction in hypertension; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; SCOPE, Study on Cognition and Prognosis in the Elderly; Val-HeFT, Valsartan–Heart Failure Trial; CHARM, Candesartan in Heart failure Assessment in Reduction of Mortality; ABCD-2C, Appropriate Blood pressure Control in Diabetics; RENAAL, Reduction of End points in Non–insulin-dependent diabetes mellitus with Angiotensin II Antagonist Losartan; IDNT, Irbesartan Diabetic Nephropathy Trial; and IRMA, Irbesartan Micro Albuminuria II Trial.

seems mainly related to the dose selected and to the duration of action of the respective drugs. Nevertheless, additional studies are needed to assess whether these differences are really clinically relevant when examining end points such as morbidity and mortality.

### Who Should be Treated With an Angiotensin II Receptor Antagonist?

Angiotensin II receptor antagonists provide a more specific blockade of the renin-angiotensin system and have better tolerability when compared with ACE inhibitors. In addition, the evidence available thus far for this new class of antagonists has established that their efficacy is equal to that of ACE inhibitors in hypertension. Therefore, it is conceivable that angiotensin II receptor blockers will take a growing place in the management of hypertensive patients. However, the place of angiotensin II antagonists in the management of hypertension will, of course, depend on the results of morbidity and mortality trials. Three studies have included patients with slightly different clinical profiles (Table 3). The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE)

trial compared a losartan-based and an atenolol-based regimen in patients with high cardiovascular risk who had electrocardiographic evidence of left ventricular hypertrophy.<sup>115</sup> In the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial, >14 000 patients were enrolled on the basis of age plus 1 to 3 other cardiovascular risk factors. In this study, valsartan was compared with amlodipine. Finally, in the Study on Cognition and Prognosis in the Elderly (SCOPE), the effects of candesartan were compared with those of a placebo in an older hypertensive population (70 to 89 years).

In patients with congestive heart failure, there is no evidence at present that angiotensin II receptor blockers are superior to ACE inhibitors. However, because of their excellent tolerability profile, angiotensin II receptor blockers may be considered in patients developing an ACE-inhibitor–induced cough. Ongoing trials, such as the Valsartan–Heart Failure Trial (Val-HeFT) and the Candesartan in Heart Failure Assessment in Reduction of Mortality (CHARM) trial, will provide more insight regarding the potential of angiotensin II receptor blockade in heart failure. They will

also address several practical issues such as dosing (once versus twice daily and monotherapy versus combination) and efficacy in different populations (ACE-inhibitor naive, ACE-inhibitor intolerant, and diastolic dysfunction). Two additional studies, the Optimal Trial in Myocardial Infarction With the Angiotensin II Antagonist Losartan (OPTIMAAL) and the Valsartan in Acute Myocardial Infarction (VALIANT) trial, will be conducted in patients after a myocardial infarction. In both trials, the effects of the angiotensin II blocker (losartan in OPTIMAAL and valsartan in VALIANT) will be compared with captopril. In OPTIMAAL, losartan is given once daily as monotherapy, whereas in VALIANT, valsartan is given twice daily and in combination with an ACE inhibitor. Again, the results of these 2 trials will establish whether combination therapy is useful for optimum clinical effect.

Thus far, there is also no evidence that angiotensin II receptor blockers are superior to ACE inhibitors in treating patients with diabetic and nondiabetic nephropathies. Therefore, at the present time, ACE inhibitors must be considered the first-line choice in these indications, with angiotensin II receptor blockers as a valuable substitute in cases of intolerance to ACE inhibitors. Several trials are now exploring the potential of angiotensin II receptor blockers in patients with renal diseases. In a study on renal protection and losartan, the Reduction of End Points in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) trial, losartan was compared with the usual care in patients with type II diabetes and diabetic nephropathy. Usual care comprises diuretics, vasodilators, and/or  $\beta$ -blockers to achieve a target blood pressure of <140/90 mm Hg. The Irbesartan Diabetic Nephropathy Trial (IDNT) has a comparable objective but, in this trial, irbesartan was compared with amlodipine and usual therapy in 3 parallel groups. Finally, the Appropriate Blood Pressure Control in Diabetics (ABCD-2V) trial will evaluate the impact of valsartan in the treatment of normotensive and hypertensive patients with non-insulin-dependent diabetes mellitus.

### Future Developments

In the management of patients with congestive heart failure and those with renal diseases, high doses of ACE inhibitors are often necessary to block the renin-angiotensin system completely and, hence, to obtain the maximal benefits of blocking the renin-angiotensin system. In these situations, the combination of an ACE inhibitor and an AT<sub>1</sub> receptor antagonist could seem attractive to improve the overall blockade of the system.<sup>116</sup> However, except for economic reasons, it seems questionable to attempt complete blockade of the renin-angiotensin system by a combination of an ACE-inhibitor with an AT<sub>1</sub> receptor antagonist if the same result could be achieved by a higher dose of an AT<sub>1</sub> receptor antagonist alone without adding the side effects inherent to all ACE inhibitors. Several studies were conducted in patients with hypertension, renal diseases, and heart failure to evaluate the combination of an ACE inhibitor and AT<sub>1</sub> receptor antagonist.<sup>117-121</sup> These studies have provided conflicting results: some studies suggested a beneficial effect of the combination, whereas others did not. The main limitation of

these early studies is that the full dosing ranges of the AT<sub>1</sub> receptor blockers and/or ACE inhibitors were not explored. Thus, one cannot ascertain that the same effect could have been obtained with a higher dose of the antagonist alone. Some of the large clinical trials discussed previously will address this specific question, particularly in heart failure.

### Conclusions

There is now convincing evidence that the new class of specific, angiotensin II receptor antagonists is as effective as ACE inhibitors,  $\beta$ -blockers, calcium antagonists, and diuretics in treating patients with mild to moderate hypertension. However, these antagonists are characterized by a better tolerability profile. In contrast to most other recent classes of antihypertensive drugs, a large number of outcome trials have been initiated to evaluate angiotensin II antagonists. Their results will demonstrate whether angiotensin II receptor antagonists can prevent target organ damage and reduce cardiovascular morbidity and mortality. They will also enable the more appropriate definition of the role of these antagonists in the management of patients with hypertension, heart failure, or renal diseases.

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