New drug classes

Angiotensin II receptor antagonists

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Blockade of the renin-angiotensin system began as a way of studying the pathogenesis of cardiovascular disease with specific pharmacological probes. Oral activity, achieved by shortening the original peptide structures, transformed the probes into therapeutic agents, the angiotensin-converting enzyme (ACE) inhibitors. However, ACE is a non-specific target for blocking the renin-angiotensin enzymatic cascade. The availability of orally active drugs turned ACE inhibition into a therapeutic breakthrough but more specific blockade always seemed desirable. This goal has now been achieved with the orally active angiotensin II receptor antagonists; six are on the market and more are under development. This new class of drugs is equal in efficacy to ACE inhibitors, at least in hypertensive patients. Trials now underway will demonstrate whether angiotensin II receptor antagonists can prevent target-organ damage and reduce cardiovascular morbidity and mortality. If they do, these compounds might one day replace ACE inhibitors.

It is now 100 years since renin was described by R Tigerstedt and P G Bergmann as a pressure system originating in the kidney and more than 60 years since H Goldblatt’s group demonstrated that hypertension could be generated in dogs by the constriction of one renal artery, a procedure which in 1940 was shown to stimulate renin (angiotensin) production by the ischaemic kidney. Then the elements of the enzymatic cascade representing the renin-angiotensin system were progressively elucidated (figure 1). In the 1970s came the first observations that angiotensin II harms the heart and kidney and that patients with high levels of plasma-renin activity are at increased risk of stroke or myocardial infarction.

The development of pharmacological agents that block the renin-angiotensin system specifically have helped to define the contribution of this system to blood-pressure control and to the pathogenesis of hypertension, congestive heart failure, and chronic renal failure. The concept of treating hypertension and heart failure via this route was first established in the 1970s with saralasin, a peptidic antagonist of angiotensin II receptors.1–3 Angiotensin II receptor blockade with saralasin, alone or in combination with salt depletion, lowered blood pressure in hypertensive patients and improved haemodynamics in congestive heart failure. However, saralasin had to be administered intravenously and at higher doses it had some partial agonist, angiotensin-II-like effects.

The next breakthrough came with captopril, the first orally active angiotensin-converting enzyme (ACE) inhibitor. Studies of this new approach to inhibition of the renin-angiotensin system rapidly confirmed and reinforced the seminal clinical observations made with saralasin. Today ACE inhibitors make an important contribution to the control of hypertension and to the pathogenesis of cardiovascular disease with specific pharmacological probes. Oral activity, achieved by shortening the original peptide structures, transformed the probes into therapeutic agents, the angiotensin-converting enzyme (ACE) inhibitors. However, ACE is a non-specific target for blocking the renin-angiotensin enzymatic cascade. The availability of orally active drugs turned ACE inhibition into a therapeutic breakthrough but more specific blockade always seemed desirable. This goal has now been achieved with the orally active angiotensin II receptor antagonists; six are on the market and more are under development. This new class of drugs is equal in efficacy to ACE inhibitors, at least in hypertensive patients. Trials now underway will demonstrate whether angiotensin II receptor antagonists can prevent target-organ damage and reduce cardiovascular morbidity and mortality. If they do, these compounds might one day replace ACE inhibitors.

The most recent therapeutic development is the new class of specific, nonpeptide, orally active angiotensin II receptor antagonists.

Renin-angiotensin system

Via ACE inhibitors and angiotensin II receptor antagonists the renin-angiotensin system has been characterised in greater detail (figure 1). The cascade starts with cleavage of angiotensinogen by renin to form the inactive decapeptide angiotensin I. Angiotensin I can also be generated by non-renin enzymes such as tonin or cathepsin. Thereafter, angiotensin I is converted by ACE into angiotensin II. Although other angiotensin peptides have biological effects, angiotensin II is the major end-product of the system. Alternative enzymatic pathways to ACE, such as trypsin, cathepsin, or the heart chymase, can also convert angiotensin I but how much these other enzymes contribute to the generation of angiotensin II is not clear.

These alternative routes to angiotensin II could explain why angiotensin II plasma concentrations are not completely suppressed by chronic ACE inhibition. However, we do not know if these factors play a greater role than the pharmacokinetic profile and tissue penetration of the ACE inhibitors. During long-term ACE inhibition, ACE activity is upregulated and plasma angiotensin I levels are high due to stimulated renin secretion.4 Thus, although plasma angiotensin II levels become unmeasurable during acute ACE inhibition, if
ACE activity is not fully blocked around the clock, some angiotensin II will be generated as soon as any ACE activity reappears. ACE is also called kininase II because it participates in the breakdown of bradykinin to inactive peptides. Inhibition of ACE produces an increase in plasma bradykinin, which almost certainly contributes to the side-effect profile of ACE inhibitors (eg, angio-oedema) and may play a role in the organ-specific effects of these drugs. Whether bradykinin accumulation contributes to the antihypertensive efficacy of ACE inhibitors is still debated.

**Angiotensin receptors**

The final step of the renin-angiotensin cascade is activation of angiotensin II receptors by angiotensin II. The development of specific angiotensin II receptor antagonists (figure 2) has been a crucial step in the recognition of angiotensin II receptor subtypes.12,13 The clinically important ones are types 1 and 2. AT₁ receptors are selectively inhibited by losartan and are sensitive to dithiothreitol whereas AT₂ receptors are inhibited by PD 123177 and related compounds but are insensitive to dithiothreitol. In rodents, subtypes AT₁A and AT₁B are recognised and in amphibians and in neuroblastoma cell lines, a receptor inhibited neither by losartan nor by PD 123177 has been classified as AT₃. AT₁ and AT₂ receptors12,13 belong to the superfamily of G-protein-coupled receptors that contain seven transmembrane regions. Their aminoacid sequence appears to be highly conserved across species and across tissues within a species. AT₁ and AT₂ receptors share only about 34% homology and have distinct signal transduction pathways.14,15

AT₁ receptors have been localised in the kidney, heart, vascular smooth-muscle cells, brain, adrenal glands, platelets, adipocytes, and in the placenta. AT₂ receptors are important during the development of the fetus but numbers decrease in the postnatal period.14 In adult tissues, these receptors are present only at low levels, mainly in the uterus, adrenal, central nervous system, heart (cardiomyocytes and fibroblasts), and kidney.14 AT₂ receptors appear to be re-expressed or upregulated in experimental cardiac hypertrophy, myocardial infarction and vascular and wound healing.15

All known clinical effects of angiotensin II are mediated by the AT₁ receptor (panel 1). The physiological role of the AT₁ receptor is only partly understood. Functions attributed to AT₁ receptors include inhibition of cell growth, promotion of cell differentiation, and apoptosis14,15 so AT₂ receptors could have an important role in counterbalancing some of the effects of angiotensin II mediated by AT₁ receptors. However, this topic remains controversial.14,15 There is also some recent evidence of a

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**Figure 1: Renin-angiotensin system**

ACE activity is not fully blocked around the clock, some angiotensin II will be generated as soon as any ACE activity reappears. ACE is also called kininase II because it participates in the breakdown of bradykinin to inactive peptides. Inhibition of ACE produces an increase in plasma bradykinin, which almost certainly contributes to the side-effect profile of ACE inhibitors (eg, angio-oedema) and may play a role in the organ-specific effects of these drugs. Whether bradykinin accumulation contributes to the antihypertensive efficacy of ACE inhibitors is still debated.

**Figure 2: Structures of angiotensin II receptor antagonists**

Candesartan

Losartan

Telmisartan

Valsartan

Eprosartan

Irbesartan
Panel 1: Effects of angiotensin II mediated via AT₁ and AT₂ receptor stimulation

AT₁ receptor stimulation
- Vasconstriction (preferentially coronary, renal, cerebral)
- Sodium retention (angiotensin, aldosterone production)
- Water retention (vasopressin release)
- Renin-suppression (negative feedback)
- Myocytes and smooth-muscle-cell hypertrophy
- Stimulation of vascular and myocardial fibrosis
- Inotropic/contractile (cardiomyocytes)
- Chronotropic/arrhythmogenic (cardiomyocytes)
- Stimulation of plasminogen activator inhibitor-1
- Stimulation of superanoxide formation
- Activation of sympathetic nervous system
- Increased endothelin secretion

AT₂ receptor stimulation
- Antiproliferation/inhibition of cell growth
- Cell differentiation
- Tissue repair
- Apoptosis (vasoconstriction)
- Kidney and urinary-tract development

role for AT₁ and AT₂ receptors in the development of the ureter and renal collecting system.20,21 A dysfunction of the AT₂ receptor gene appears to contribute to congenital anomalies of the kidney and urinary tract.

Pharmacology of AT₁ receptor antagonists

So far, six orally active AT₁ receptor antagonists have been accepted by the US Food and Drug Administration and launched in the USA and various European countries for the treatment of hypertension (panel 2). Others are being developed. The pharmacodynamic and pharmacokinetic characteristics are summarised in panel 3. One feature of most, if not all, AT₁ receptor antagonists is “insurmountable blockade”. This refers to the non-parallel displacement of the angiotensin II response curves seen in vitro. Vauquelin and his coworkers have convincingly demonstrated that these drugs are nevertheless competitive antagonists, with a very slow dissociation from the receptor.22,23 Since insurmountable blockade is difficult to achieve at doses used clinically, it is not further discussed in any detail.

Losartan

Losartan, the prototype highly selective AT₁ receptor antagonist, was derived from the Takeda series of 1-benzylimidazole-5-acetic acid derivatives, which are themselves weak angiotensin II antagonists.24 In rat vascular smooth muscle, losartan competes with the binding of angiotensin II to AT₁ receptors with median inhibitory concentration (IC₅₀) of 20 nmol/L. It has no affinity for the AT₂ receptor and no partial agonist properties. Losartan’s major active metabolite is EXP3174. Administered intravenously, EXP3174 is 10–20 times more potent than losartan and has a longer duration of action. On the isolated rabbit aorta, losartan produces a surmountable blockade of the contractile response induced by angiotensin II whereas EXP3174 causes an insurmountable blockade. Because the oral bioavailability of the active metabolite is very low, the drug on the market is losartan. Pharmacokinetic characteristics are presented in panel 3. Losartan and EXP3174 are excreted by the kidney and bile. Neither compound is dialysed.

Valsartan

Valsartan is a non-heterocyclic antagonist in which the imidazole of losartan has been replaced with an acylated aminoacid. It is a potent AT₁ antagonist (IC₅₀ of 2·7 nmol/L on rat aorta).25 Valsartan is excreted in the bile (70%) and by the kidney (30%). There is only one metabolite and it is inactive. Food decreases drug absorption by about 40%. Like losartan, valsartan has no affinity for adrenergic, histamine, substance P, muscarinic, and serotonin receptors. When the functional antagonism was assessed in rabbit isolated aortic strips, valsartan dose-dependently inhibited the contractions induced by angiotensin II with an apparent pKᵦ of 9·26. The dose-response curve to angiotensin II is displaced to the right by valsartan and the maximum response is reduced by about 50% suggesting insurmountable antagonism.

Irbesartan

Irbesartan is longer acting than losartan and valsartan.26 It has a high affinity for the AT₁ receptor (IC₅₀ 1·3 nmol/L in rat liver) and no affinity for AT₂ receptors. The molecule contains an imidazoline ring in which a carbonyl group functions as a hydrogen bond acceptor in place of the C5 hydroxymethyl group of losartan. Irbesartan has no active metabolite. It is cleared by the bile (80%) and kidney (20%) and its volume of distribution (53–93 L) is greater than that for losartan (12 L) and EXP 3174 (172 L). Irbesartan induces a non-competitive antagonism for AT₁ receptors.

Candesartan cilexetil

Candesartan is a potent, long-acting antagonist.27 Because of poor oral absorption of its prodrug, cilexetil was identified as the compound with the best angiotensin II antagonistic activity profile after oral administration. Candesartan dose-dependently inhibits the in vitro binding of radiolabelled angiotensin II to AT₁ receptors with a Kᵦ of 0·64 nmol/L. AT₁ binding affinity in rabbit aorta was 80 times greater than that of losartan and 10 times greater than that of EXP 3174. This drug produces an insurmountable antagonism, which reflects its tight binding to and slow dissociation from the AT₁ receptor. Candesartan has a half-life of about 9 h (up to 12 h in the elderly). It is eliminated by the kidneys (60%) and bile (40%). There is no significant drug accumulation in patients with mild renal impairment but at doses greater than 12 mg daily candesartan cilexetil may accumulate in patients with severe renal dysfunction. The mean extraction ratio for candesartan from dialysed blood is low.

Telmisartan

Telmisartan28 has a very long elimination half-life of about 24 h in patients with mild-to-moderate hypertension on daily doses of 20–160 mg for 4 weeks. Telmisartan is...
directly active; it undergoes minimal transformation and is excreted almost completely in the faeces (98%). Telmisartan demonstrated insurmountable inhibition of angiotensin-II-induced contractions in isolated rabbit aortic tissues. Because telmisartan causes an increase in serum digoxin, digoxin levels should be monitored when telmisartan is combined with digoxin. Warfarin levels may fall during coadministration with telmisartan.

**Preclinical pharmacology**

AT<sub>1</sub> receptor antagonists dose-dependently attenuate the pressor response to intravenous angiotensin II and reduce blood pressure in animal models of hypertension. They also reduce cardiac hypertrophy and improve haemodynamics in animal models of heart failure. They increase sodium excretion and diuresis and lower blood pressure more effectively than placebo without affecting heart rate, and do so regardless of sex, race, or age. Dose-dependent reductions in blood pressure at trough drug concentrations have been obtained with only some of these drugs, while dose-dependent inhibition of the pressor effect of angiotensin II in normotensive individuals has been a consistent finding. This apparently flat dose-response relation may be explained by failure to explore fully the lower and the upper extremes of the dose-response curve. When irbesartan was investigated across a large range of doses, there was a clear dose-response for both reduction in blood pressure and percentage of patients achieving a therapeutic response.

Long-term studies have demonstrated that angiotensin II antagonists and ACE inhibitors have comparable efficacy in terms of blood-pressure reduction at trough. During the initial days of treatment, ACE inhibitors are sometimes more effective, perhaps because of the high protein binding of the angiotensin II antagonists. This new class of drugs are also as effective as calcium-channel blockers, and beta-blockers and when evaluated, as hydrochlorothiazide. Blood pressure becomes salt-dependent when the renin-angiotensin system is blocked so a diuretic is often combined with an ACE inhibitor. Similarly, combining a thiazide diuretic with an angiotensin II receptor antagonist results in an additional lowering of blood pressure.

**Are there differences between angiotensin II receptor antagonists?**

These drugs have the same mechanism of action but different pharmacokinetic profiles, which may account for potential differences in efficacy. Also the starting dose may have been chosen on different criteria. When the recommended starting doses of losartan (50 mg), valsartan (80 mg), and irbesartan (150 mg) were compared for their ability to block the blood pressure response to exogenous angiotensin II in healthy volunteers, irbesartan exhibited the greatest inhibition of the renin-angiotensin system, at peak as well as at trough concentrations.

A meta-analysis of 43 randomised placebo-controlled trials suggests comparable antihypertensive efficacy within this class of drugs. Some head-to-head comparisons of two drugs from this class have been done in patients with mild-to-moderate hypertension. One study demonstrated that losartan and valsartan induced comparable decreases in blood pressure at trough concentrations but a higher response rate was suggested with valsartan 160 mg than with losartan 100 mg. 24 h blood pressure control was also more effective with valsartan 80 mg than losartan 50 mg. In another study, candesartan 8 and 16 mg was also more effective with valsartan 80 mg than losartan 50 mg.

### Panel 3: Pharmacokinetic properties

<table>
<thead>
<tr>
<th>Drug</th>
<th>In-vitro AT&lt;sub&gt;1&lt;/sub&gt; receptor affinity&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Bioavailability (%)</th>
<th>Food effect</th>
<th>Active metabolite</th>
<th>Half-life (h)</th>
<th>Protein binding (%)</th>
<th>Daily dosage (mg)</th>
</tr>
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<tbody>
<tr>
<td>Losartan (EXP 3174)</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt;:20 nmol/L</td>
<td>33</td>
<td>No</td>
<td>Yes</td>
<td>2 (6–9)</td>
<td>98–7 (99–8)</td>
<td>50–100</td>
</tr>
<tr>
<td>Valsartan</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt;:2.7 nmol/L</td>
<td>25</td>
<td>Yes (~–40%)</td>
<td>No</td>
<td>9</td>
<td>95</td>
<td>80–320</td>
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<tr>
<td>Irbesartan</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt;:1.3 nmol/L</td>
<td>70</td>
<td>No</td>
<td>No</td>
<td>11–15</td>
<td>90&lt;sup&gt;b&lt;/sup&gt;</td>
<td>150–300</td>
</tr>
<tr>
<td>Candesartan cilexetil</td>
<td>TCV 116</td>
<td>—</td>
<td>No</td>
<td>Yes</td>
<td>3–5–4</td>
<td>—</td>
<td>4–16 (32)</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>K&lt;sub&gt;i&lt;/sub&gt;:3.7 nmol/L</td>
<td>43</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>&gt;99</td>
<td>40–80</td>
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<tr>
<td>Eprosartan</td>
<td>Eprosartan IC&lt;sub&gt;50&lt;/sub&gt;:1</td>
<td>15</td>
<td>No</td>
<td>No</td>
<td>5–7</td>
<td>98</td>
<td>400–800</td>
</tr>
</tbody>
</table>

<sup>a</sup>IC<sub>50</sub> = concentration displacing specifically 50% of the binding of angiotensin II; K<sub>i</sub> = inhibition constant.

<sup>b</sup>Some studies suggest that irbesartan has a greater protein binding (>95%).

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**NEW DRUG CLASSES**

**Clinical pharmacology**

Angiotensin II receptor antagonists have been available for the treatment of hypertension for 5 years and they have been thoroughly evaluated for their efficacy in mild, moderate, and severe hypertension. All six drugs lower blood pressure more effectively than placebo without affecting heart rate, and do so regardless of sex, race, or age. Dose-dependent reductions in blood pressure at trough drug concentrations have been obtained with only some of these drugs, while dose-dependent inhibition of the pressor effect of angiotensin II in normotensive individuals has been a consistent finding. This apparently flat dose-response relation may be explained by failure to explore fully the lower and the upper extremes of the dose-response curve. When irbesartan was investigated across a large range of doses, there was a clear dose-response for both reduction in blood pressure and percentage of patients achieving a therapeutic response. Long-term studies have demonstrated that angiotensin II antagonists and ACE inhibitors have comparable efficacy in terms of blood-pressure reduction at trough. During the initial days of treatment, ACE inhibitors are sometimes more effective, perhaps because of the high protein binding of the angiotensin II antagonists. This new class of drugs are also as effective as calcium-channel blockers, and beta-blockers and when evaluated, as hydrochlorothiazide. Blood pressure becomes salt-dependent when the renin-angiotensin system is blocked so a diuretic is often combined with an ACE inhibitor. Similarly, combining a thiazide diuretic with an angiotensin II receptor antagonist results in an additional lowering of blood pressure.

The drugs have the same mechanism of action but different pharmacokinetic profiles, which may account for potential differences in efficacy. Also the starting dose may have been chosen on different criteria. When the recommended starting doses of losartan (50 mg), valsartan (80 mg), and irbesartan (150 mg) were compared for their ability to block the blood pressure response to exogenous angiotensin II in healthy volunteers, irbesartan exhibited the greatest inhibition of the renin-angiotensin system, at peak as well as at trough concentrations.

A meta-analysis of 43 randomised placebo-controlled trials suggests comparable antihypertensive efficacy within this class of drugs. Some head-to-head comparisons of two drugs from this class have been done in patients with mild-to-moderate hypertension. One study demonstrated that losartan and valsartan induced comparable decreases in blood pressure at trough concentrations but a higher response rate was suggested with valsartan 160 mg than with losartan 100 mg. 24 h blood pressure control was also more effective with valsartan 80 mg than losartan 50 mg. In another study, candesartan 8 and 16 mg was also more effective with valsartan 80 mg than losartan 50 mg.
the blood-pressure lowering effect of candesartan 16 mg was significantly more pronounced than that of losartan. With ambulatory blood pressure monitoring, candesartan 8 and 16 mg provided a more lasting antihypertensive effect than losartan 50 mg and 100 mg. Two double-blind studies have compared irbesartan with losartan. Irbesartan 300 mg reduced trough blood pressure to a greater extent than losartan 100 mg. Effects at peak concentrations were not investigated. In the other study, hypertensive patients were randomised to losartan 50 mg or irbesartan 150 mg and the dose was doubled for patients whose diastolic blood pressure was still above 90 mm Hg after weeks. After 8 weeks, the mean change in diastolic blood pressure at the time of trough drug concentrations was significantly greater in patients receiving irbesartan. In another randomised study in 207 hypertensive patients, telmisartan 40 and 80 mg administered for 6 weeks reduced 24 h ambulatory blood pressure significantly more than losartan 50 mg, especially during the final 6 h of the dosing interval.

These results suggest that irbesartan, candesartan, and telmisartan may be slightly more effective than losartan, the difference being related to the doses selected the durations of action of the drugs. Whether these differences are clinically relevant, in terms of morbidity and mortality, remains to be seen.

Safety and tolerability

Several thousands of patients have taken part in double-blind controlled studies evaluating the antihypertensive efficacy of the various angiotensin II receptor antagonists. A characteristic of this class of drugs is an adverse-effect profile comparable with that seen in the placebo groups; none of the six drugs reviewed here has a specific, dose-dependent adverse effect that can be attributed to the drug itself.

Because cough is seen as a class effect of ACE inhibitors, studies with these new drugs have specifically addressed this possibility. The frequency of cough in patients taking losartan, valsartan, or telmisartan was found to be significantly lower than that observed in patients on lisinopril and comparable with that seen in those on a diuretic or placebo. Also spontaneously reported cough was unusual in placebo-controlled studies. Angio-oedema, another side-effect of ACE inhibitors, seems to be related to the accumulation of bradykinin but this may not be the only mechanism. Some cases of angio-oedema have been reported with losartan. However, because angio-oedema may occur with many substances, including other drugs and some foods, it is not clear if these published cases of angio-oedema really are linked to the drug.

First-dose hypotension is often encountered when ACE inhibitors are given to salt-depleted or hypovolaemic patients. First-dose hypotension is not seen when angiotensin II antagonists are given to diuretic-treated hypertensive patients, probably because of these drugs' slower onset of action. Even in elderly patients, who are more susceptible to first-dose hypotension, no orthostatic hypotension was seen with candesartan. Because plasma angiotensin II levels increase markedly during angiotensin II receptor blockade, rebound hypertension was initially a matter of concern if drug therapy was acutely withdrawn. However, studies with losartan and irbesartan have demonstrated that rebound hypertension is not a problem.

In patients with mild-to-moderate hypertension taking part in the clinical trials, kidney function was not adversely affected, and even in the presence of chronic renal insufficiency, angiotensin II antagonists are generally well tolerated, probably because they are cleared largely in the bile. Preliminary results suggest that, as with ACE inhibitors, acute renal failure may occur if angiotensin II antagonists are administered to patients with renal artery stenosis or diffuse intrarenal vascular stenosis. In patients with heart failure, the incidence of renal dysfunction and hyperkalaemia was also comparable in losartan and captopril treated patients.

Angiotensin II antagonists have no major impact on routine laboratory indices. Occasional minor increases in liver enzymes were usually transient. Slight increases in serum potassium have been reported during angiotensin II receptor blockade. Like ACE inhibitors, angiotensin II antagonists lower the in post-transplant erythrocytosis. Losartan, but not the other angiotensin II antagonists, increases urinary uric acid excretion. This is due to a specific effect of losartan potassium on urate transport in the renal proximal tubule and is nothing to do with angiotensin II receptor blockade. Angiotensin II antagonists are contraindicated in pregnancy and should not be used in breastfeeding mothers.

Cardiac and renal effects

Renin-angiotensin system inhibition with an ACE inhibitor is currently a recommended approach for the management of heart failure and appears to be very effective for left-ventricular hypertrophy in hypertensive patients. A recent study with valsartan shows that this angiotensin II antagonist also produces a significant regression of left-ventricular hypertrophy in previously untreated patients with essential hypertension. In heart failure, short-term studies indicate that AT1 receptor antagonists improve haemodynamic indices and are well tolerated, and preliminary studies suggest that AT1 receptor antagonists are at least as effective as ACE inhibitors but with a more favourable side-effect profile.

The ELITE trial (Evaluation of Losartan In the Elderly) compared captopril 50 mg three times daily and losartan 50 mg daily in elderly patients with heart failure, renal safety being the primary endpoint. No difference between the drugs in the incidence of renal dysfunction was found but after 1 year of follow-up, a secondary endpoint (combined mortality from and hospital admission for heart failure) was lower in the losartan group. Preliminary results of the bigger ELITE II follow-up trial confirm that patients treated with losartan had significantly less side-effects than those on the ACE inhibitor. However, there were slightly, but not significantly, more deaths in the group treated with losartan. Unfortunately, the trial was designed to demonstrate superiority of losartan and was not powered to establish equal efficacy of the two drug classes. Also the losartan dose was too small; losartan 50 mg blocks the AT1 receptors significantly less than irbesartan 150 mg does. It would be wrong to conclude from ELITE II that the class of angiotensin receptor antagonists is less effective than ACE inhibitors in the treatment of congestive heart failure.

The experimental and small clinical studies indicate that angiotensin II receptor antagonists have effects on kidney function similar to those of ACE inhibitors. They have no influence on glomerular filtration rate and they
Panel 4: Clinical trials in progress with angiotensin II receptor antagonists

<table>
<thead>
<tr>
<th>Drug</th>
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<th>No</th>
<th>Population</th>
<th>Endpoint</th>
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<td>Losartan</td>
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<td>Heart failure</td>
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<td>Mortality, MI, stroke</td>
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<td></td>
<td>OPTIMAL</td>
<td>5000</td>
<td>Post-MI with LV dysfunction</td>
<td>All-cause mortality</td>
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<td>RENAL</td>
<td>1520</td>
<td>NIDDM patients with nephropathy</td>
<td>Composite of ESRD, doubling of creatinine, mortality</td>
<td>2001</td>
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<td>ValHeFT</td>
<td>5200</td>
<td>Heart failure</td>
<td>All-cause mortality</td>
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<td></td>
<td>VALIANT</td>
<td>14 500</td>
<td>Post-MI with LV dysfunction</td>
<td>All-cause mortality</td>
<td>2005</td>
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<td>14 400</td>
<td>Hypertensives with high risk</td>
<td>Cardiovascular mortality</td>
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<td>CHARM I</td>
<td>1700</td>
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<td>Composite of ESRD, doubling of creatinine, mortality</td>
<td>2000</td>
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<td></td>
<td>IRMA II</td>
<td>611</td>
<td>NIDDM in hypertensives</td>
<td>Microalbuminuria</td>
<td>2000</td>
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LVH=left ventricular hypertrophy; MI=myocardial infarction; NIDDM=non-insulin-dependent diabetes mellitus; ESRD=end-stage renal disease; EF=ejection fraction; ACE=ACE inhibitor.

increase renal blood flow.68–69 This renal haemodynamic response was found in normotensive and hypertensive individuals. A natriuretic effect, which seems to be sustained after chronic administration,68 is abolished by the concomitant administration of indomethacin.61 In diabetic and non-diabetic proteinuric or microalbuminuric patients, ACE inhibitors reduce urinary protein excretion and have a favourable impact on long-term renal function.88–90 Preliminary studies with the angiotensin II receptor antagonists suggest that these agents also decrease filtration fraction and reduce urinary albumin excretion.11,14,49,52,53

Combining AT1 receptor antagonist with ACE inhibitors

Because of the pharmacokinetic properties of ACE inhibitors and the possibility that angiotensin II is generated by non-ACE pathways, there is a frequent concern about incomplete blockade of the renin-angiotensin system with ACE inhibitors. Additional efficacy might be expected theoretically from a combination of an ACE inhibitor with an AT1 receptor antagonist but if the antagonist blocks all the effects of angiotensin II independently of circulating angiotensin II in the circulation, ACE inhibition might not be necessary. However, angiotensin II levels do increase during chronic blockade of AT1 receptors39 and can be expected to compete with the antagonist at the receptor site and to displace it. If so, an ACE inhibitor could blunt the rise in angiotensin II and so increase the antihypertensive efficacy of the receptor antagonist. Whether this hypothesis holds true clinically and whether high circulating angiotensin II levels are indeed able to compete with the mostly insurmountable receptor blockade are questions that deserve further investigation.

A blunting of the reactive rise in circulating angiotensin II might also decrease the efficacy of angiotensin II blockers by causing less AT1 receptor stimulation. This drug combination would add the effects of bradykinin accumulation to those of AT1 receptor blockade. Bradykinin accumulation does contribute to the side-effect profile of ACE inhibitors but whether the changes in bradykinin levels have a role in the beneficial properties of ACE inhibitors is less well documented.

ACE inhibitor/AT1 receptor antagonist combinations have been studied in renal diseases and heart failure. Experiments in rats with renal mass ablation showed no advantage for the combination beyond blood-pressure control.11 However, observations on a few patients suggest that a more important decrease in proteinuria can be obtained with the combination in hypertensive patients with diabetic nephropathy and in normotensive patients with IgA nephropathy and proteinuria.95,96 High doses of angiotensin II antagonists were not investigated.

In congestive heart failure, high doses of ACE inhibitors are often necessary and combining an ACE inhibitor with an AT1 receptor antagonist might seem attractive.97–101 Preliminary studies have shown that a combination of losartan and enalapril is well tolerated in patients with heart failure and that the combined therapy results in greater effect in terms of suppression of aldosterone and norepinephrine than enalapril alone.97 Similar results have been reported for valsartan102 and candesartan.96 In patients with anterior myocardial infarction, losartan 25 mg per day combined with captopril 75 mg is well tolerated and seems to be more effective than captopril alone.100 Again, full dose ranges of the AT1 receptor blockers were hardly explored.

Large clinical trials are needed to decide whether the combination provides additive benefits in patients with heart failure or chronic renal failure. However, to demonstrate any advantages for an ACE inhibitor/AT1 receptor combination, the comparison should be with a full titration of each individual drug; also long-acting antagonists are used. Economic reasons apart, it seems questionable to attempt complete blockade of the renin-angiotensin system by combining an ACE inhibitor with an AT1 receptor antagonist if the same result can be achieved by a higher dose of an AT1 receptor antagonist alone.

Ongoing clinical trials

Blood pressure, proteinuria, left-ventricular hypertrophy, and haemodynamics are surrogate endpoints and large clinical trials are underway to establish the morbidity and mortality benefits of specific AT1 receptor blockade in patients with hypertension, chronic renal failure, or heart failure (panel 4). These studies102–104 should also help to determine whether the mechanistic differences between ACE inhibitors and angiotensin II blockers lead to significant clinical differences, and they may provide further information on the potential benefits of the combination of ACE inhibitors and angiotensin II blockers.

Three large trials of angiotensin II antagonists in hypertension include patients with slightly different clinical profiles. LIFE (Losartan Hypertension Survival Study) compares a losartan-based with an atenolol-based
regimen in patients with electrocardiographic evidence of left-ventricular hypertrophy, most of whom have one or more other cardiovascular risk factors, such as coronary heart disease or diabetes.\textsuperscript{103,104} In VALUE (Valsartan Antihypertensive Long-Term Evaluation) more than 14,000 patients have been enrolled on the basis of age plus one to three other cardiovascular risk factors.Valsartan is compared with amlodipine. In SCOPE (Study on Cognition and Prognosis in the Elderly) candesartan is compared with placebo in hypertensive patients (aged 70–80). The placebo group will receive a diuretic whenever needed to achieve the goal of a blood pressure below 160/85 mm Hg. A mini mental state examination will be used to assess the impact on cognitive function.

The Val-Heft and CHARM trials should tell us more about the potential for angiotensin II receptor blockade in heart failure,\textsuperscript{10,11} and they will also address practical issues such as once vs twice daily dosing, monotherapy vs combination therapy, and efficacy in different populations (ACE-inhibitor naive, ACE-inhibitor intolerant, diastolic dysfunction). OPTIMAAL and VALIANT\textsuperscript{12} are trials in post-myocardial infarction,\textsuperscript{103,104} Losartan (OPTIMAAL) and valsartan (VALIANT) are being compared with captopril. Losartan is once-daily monotherapy whereas valsartan is given twice daily and in combination with an ACE inhibitor.

Three other trials are testing angiotensin II receptor antagonists in non-insulin-dependent diabetic nephropathy. In RENAAL (Losartan Renal Protection study) losartan is compared with 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 below 140/90 mm Hg. The Irbesartan Diabetic Nephropathy Trial (IDNT) has a similar objective but irbesartan is compared with captopril. Irbesartan is once-daily monotherapy whereas valsartan is given twice daily and in combination with an ACE inhibitor.

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