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Scientific Update™

Angiotensin II AT_1 Receptor Blockers: Are there differences that might affect outcome?

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Atherosclerotic coronary heart disease, stroke and renal failure are complications of systemic hypertension and result from vascular injury mediated by multiple mechanisms. A common mediator causing arterial damage in hypertension is activation of the tissue renin angiotensin system. Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II AT_1 receptor blocking agents (ARBs) interfere with the actions of angiotensin II and are becoming an increasingly important treatment in the prevention of target organ damage. ARBs directly interfere with the adverse arterial remodeling effects of angiotensin II by preventing smooth muscle cell growth, limiting the stimulation of oxidative stress-induced vascular damage, and reversing the abnormal collagen/elastin ratio found in hypertensive arteries. ACEIs have been shown to normalize small artery remodeling in hypertensive patients, and so far, preliminary evidence from animal data suggests that ARBs may have a similar beneficial effect.

The need for improved blood pressure control

The benefit of lowering blood pressure beyond previously accepted targets to prevent adverse cardiovascular outcomes has been demonstrated by the recently published HOT study.[1] This study demonstrated a 51% reduction in major cardiovascular events in diabetic subjects with target diastolic blood pressures of < 80 mm Hg, as compared to patients targeted to the < 90 mm Hg group. Yet, throughout the world, blood pressure control remains far from current targets and no where near the goals suggested by the HOT study. Despite increased awareness of hypertension and the need for treatment, the proportion of patients adequately controlled has not improved (Table 1).[2]

A recent evaluation of blood pressure control in an elderly population showed that more than 40% of subjects had a blood pressure >160/90, despite more than six hypertension-related visits/year to their physician.[3] The study concluded that adequacy of blood pressure control was related to the intensity of treatment, a measure that took into account changes in treatment that occurred in response to measured blood pressure and the frequency of visits. Physicians appeared to be insufficiently aggressive with blood pressure control and failed to alter medications for about three-quarters of visits in which elevated blood pressures were recorded.

Reasons for inadequate control of blood pressure include both physician and patient determined factors. Physicians are often unwilling to increase medications because of the fear of side effects, and consequently accept

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lower target pressures. Patients show poor compliance when taking medications for a condition associated with either none or minimal symptoms, especially if the medication is associated with side effects or requires multiple daily doses.

Angiotensin II AT_1 receptor blocking drugs

Angiotensin II AT_1 receptor blockers (ARBs) are effective agents in the management of hypertension with equivalent potency to ACEIs, calcium channel blockers (CCBs) and beta-blockers. However, they have a comparable side effect profile to placebo and are consequently taken with better compliance than ACEIs, CCBs, or diuretics. In a recent comparison of irbesartan with placebo, side effects such as cough, musculoskeletal pain, and dizziness were identical to placebo. Unlike ACE inhibitors, angiotensin II AT_1 receptor blocking agents do not provoke cough (incidence of cough: enalapril 13.1%, irbesartan 2.5% in one study and enalapril 15%, losartan 3.0% in another study). However, headache occurred more frequently in placebo-treated patients than in those receiving irbesartan (placebo 16.7%, irbesartan 12.7%),[4] suggesting that hypertensive subjects may not be as asymptomatic as is often thought. Increasing the dose of irbesartan resulted in greater blood pressure lowering and a persistently better side effect profile than the placebo-treated patients.

If necessary, improved blood pressure control can be achieved with combination therapy. Combinations of ACEIs and CCBs and ACEIs and thiazide diuretics have been shown to result in a higher proportion of patients with adequately controlled blood pressure. Lower target pressures were achieved in the HOT study[1] with the use of combination therapy, the benefits being improved cardiovascular outcomes. In a recent study of irbesartan, systolic blood pressure (SBP) reductions of 12.0 mm Hg were achieved with irbesartan 300 mg daily, but reduction in SBP increased to 20.5 mm Hg when this ARB was combined with hydrochlorothiazide 12.5 mg daily.[5] Target blood pressures are more likely to be achieved with less adverse side effects when using combinations such as these.

Blood pressure control needs to be maintained throughout 24 hours and should limit the early morning surge of pressure that occurs with the same timing as acute cardiovascular complications such as myocardial infarction and unstable angina. Furthermore, to achieve patient compliance, a medication that achieves 24-hour control of blood pressure that can be administered once daily will be better accepted than one requiring a twice-daily regimen.

Table 1: Awareness and treatment of hypertension 1976-94

	1976	1988-91	1991-94
Awareness of hypertension	51%	73%	68.4%
Treated hypertensives	31%	55%	53.6%
Adequate BP control (BP<150/90)	10%	29%	27.6%

(NHANES[2])

When the time courses of the receptor blocking activity of ARBs are compared, differences in activity make longer-acting agents such as irbesartan and candesartan more suitable for once-daily administration than the other agents. Differences in pharmacokinetics are substantial (Table 2), with irbesartan having the longest half-life, the greatest bioavailabilty, and the largest volume of distribution. The shorter acting agents valsartan and losartan show surmountable and competitive receptor binding, whereas the longer acting agents candesartan and irbesartan are characterized by insurmountable and noncompetitive antagonism. This difference is probably due to the dissociation kinetics of the antagonist from the receptor, with slow dissociation kinetics causing apparently insurmountable antagonism and longer duration of action. Currently, the clinical implications of insurmountable binding are unknown.

Comparative pharmacology of the ARBs

Recent human studies have shown that the ARBs have different affinities for and occupancy of the AT_1 receptor and also differ in their duration of action. In studies in normal subjects, Belz et al have used the pressor response from increasing doses of angiotensin II to construct a dose response curve before and after the administration of the ARB.[6] The shift of the angiotensin II dose response curve resulting from ARB treatment is expressed as the ratio of

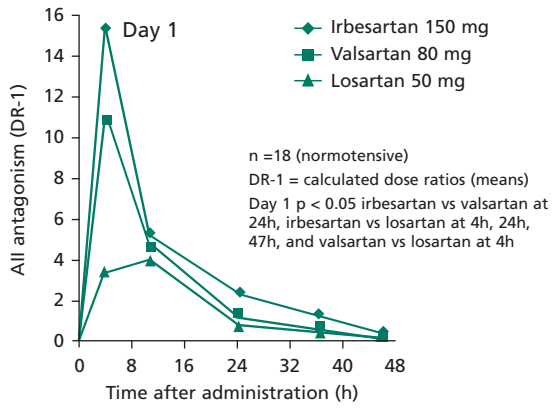
Table 2: Comparative pharmacology of ARBs

Compound	Active metabolite	Half-life (h)	Volume of distribution (L)	Bioavailability (%)	Daily dose
Valsartan	No	5-9	17	23	80-160 mg
Losartan	Yes	6-9	34	33	50-100 mg
Candesartan	Prodrug	9	9	15	8-16 mg
Irbesartan	No	11-15	53-93	60-80	150-300 mg

doses for the shifted dose response curves (DR-1). ARBs were administered (irbesartan 150 mg, valsartan 80 mg, and losartan 50 mg) as single daily doses and dose response curves were measured for periods of up to 48 hours after the administration of the medication. The results shown in Figure 1 illustrate that irbesartan had a greater overall effect on displacing the dose response curve than either valsartan or losartan, and its effect persisted for up to 36 hours after administration. Furthermore, the same group, using a rat lung radio-receptor assay, showed that irbesartan achieved much greater receptor occupancy for the same plasma concentration of drug than either losartan or valsartan (Figure 2).[7]

These studies concluded that there are important and clinically relevant differences between the ARBs, not only in their AT_1 receptor blocking potency, but also in their pharmacodynamic duration of action. This may explain why irbesartan results in significantly greater reductions in trough blood pressure than losartan.[8,9]

Figure 1: Comparisons between the effects of different ARBs on pressor dose responses to angiotensin II in man[6]

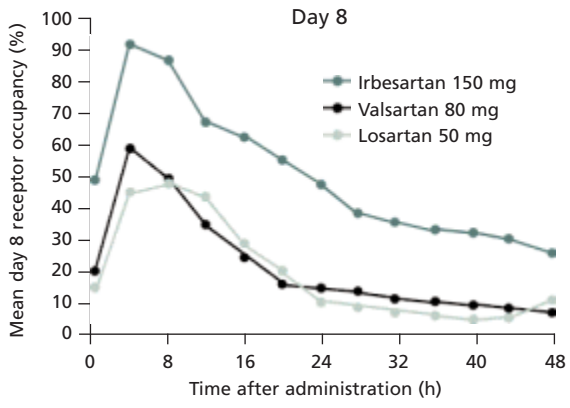


End organ protection and ARBs

Inhibiting the effect of angiotensin II is an important means of preventing end organ damage to the heart, blood vessel, kidney and brain. Left ventricular hypertrophy, atherosclerosis, heart failure, stroke and nephropathy are evidence of end organ damage in which angiotensin II plays a role.

Both ACEIs and ARBs reduce both blood pressure and left ventricular hypertrophy to similar degrees in spontaneously hypertensive rats. Irbesartan has been shown to be more effective than atenolol in reducing LVH in hypertensive patients, but little human data is available comparing the effects of ACEIs and ARBs. Angiotensin II appears to play an important role in the development of atherosclerosis with inhibition of AT_1 receptors significantly reducing atherosclerosis in animal models. However, there is no human evidence yet to show that ARBs either reduce atherosclerosis or prevent acute coronary events.

Figure 2: Angiotensin AT_1 receptor occupancy: Comparisons among ARBs[7]



The ELITE study compared treatment with the ACEI captopril and the ARB losartan in elderly subjects with moderately severe heart failure. Although the primary endpoint of renal dysfunction did not differ between the treatment groups, all cause mortality was reduced by 30% in patients allocated to losartan compared to the captopril-treated group. Although this result is compatible with the potential benefits of AT_1 receptor inhibition, the outcome of further studies such as ELITE 2 is awaited in support of this observation.

Both ACEIs and ARBs are effective at reducing blood pressure and renal protein excretion. Although ACEIs have been shown to delay the progression of renal disease in both diabetic and nondiabetic nephropathy, the results of studies using ARBs (The Irbesartan Diabetic Nephropathy Trial [IDNT] and the Losartan Renal Protection Study) are awaited. The basic science evidence is supportive for ARBs to have similar renoprotective effects as ACEIs. It is likely that ARBs cause less renal insufficiency and hyperkalemia than ACEIs, probably because of the absence of the additional bradykinin-induced vasodilation of the efferent arteriole in ACEI-treated patients. Consequently, it is probable that the ARBs will be safer and easier to use than ACEIs in patients with renal insufficiency.

Role of ARBs in the management of hypertension

If blood pressure control is to make an impact on coronary heart disease, it must be considered in the context of a multisystem disorder of lipid and glucose metabolism, with associated endothelial dysfunction resulting in the development of atherosclerosis. Thus, blood pressure control might be expected to reduce the incidence of coronary heart disease only if attention is paid to controlling the other components of the disease process. Endothelial dysfunction, central to the development and progression of atherosclerosis, is improved not only by blood pressure control, but also by reduction of LDL, improved diabetic control and hormone replacement therapy.

Conclusion

Hypertension is a major modifiable risk factor for cardiovascular disease and recent studies emphasize the benefits of control to levels not usually achieved. This goal is especially important in groups of patients at higher risk. Angiotensin II AT_1 receptor blocking agents, alone or in combination with other agents, provide treatment with a high therapeutic success. They are well-tolerated, and have the potential added benefit of adding vascular protection that is independent from the blood pressure lowering effect. The choice of an agent with pharmacodynamic properties that extends both the duration and effectiveness of vascular protection may result in improved outcomes. These benefits remain to be proven in controlled clinical trials.

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