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Scientific Update™

Targeting Blood Pressure Goals and End-Organ Protection: Advances in Renin-Angiotensin System Blockade

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Inhibition of the renin-angiotensin system (RAS) has become the cornerstone of the therapy for some of the most prevalent cardiovascular and renal diseases. In addition to initial studies that demonstrated the benefits of angiotensin-converting enzyme (ACE) inhibition in patients with heart failure due to systolic dysfunction of the left ventricle,[1-4] and the many landmark studies in patients with hypertension or renal disease, we now have the recently released Heart Outcomes Prevention Evaluation (HOPE) Trial which extended the benefits of ACE inhibition to high-risk populations such as diabetics and patients with vascular events in the absence of left ventricular dysfunction.[5] The phenomenon of "angiotensin II escape" (ie, the known increase in plasma angiotensin II that occurs in patients receiving long-term therapy with ACE inhibitors), and the discovery that enzymes other than ACE can generate angiotensin II at the local tissue level using angiotensin I or even angiotensinogen as a substrate, have led to the reasonable conclusion that angiotensin II type 1 receptor blockers (ARBs) may be a better way to antagonize the RAS.[6,7]

The undeniable clinical success of the ACE inhibitors, despite the generation of angiotensin II by non-ACE pathways, prompted a number of important studies that examined alternative mechanisms of action of these effective agents. It appears that in situations as diverse as human hypertension or animal models of cardiac remodeling following myocardial infarction (MI), an alternate role of ACE – that is, functioning as a kininase – may explain many of the beneficial effects of the inhibitors.[8,9] Indeed, ACE inhibition results in the preservation of bradykinin, a highly vasoactive peptide that stimulates the production of nitric oxide (NO) in the endothelium and is associated with potent vasodilatory, antihypertrophic, and antiproliferative effects, but which is likely to be responsible, at least in some patients, for the adverse effects of cough and angioedema.

The recent introduction of multiple, highly specific ARBs that act by blocking the binding of angiotensin II to the AT-1 receptor has been a welcome addition to existing cardiovascular therapies. These agents are effective at lowering blood pressure while maintaining an excellent, indeed placebo-like, tolerability profile. This property may be particularly important in the management of hypertension, a condition that silently causes end-organ damage in most patients, with very little (if any) associated symptoms until the manifestations of the disease are quite advanced. Therefore, antihypertensive agents that are well tolerated are likely to lead to enhanced adherence to therapy and potentially better long-term organ protection. As well, there is little doubt that because they have a more specific mechanism of action, ARBs are a more effective way of blocking the effects of angiotensin II on the AT-1 receptor than the ACE inhibitors. This blockade may eventually be proven to lead to a better prevention of adverse clinical outcomes, but it did not in the only comparative heart failure trial completed to date. As well, there are no

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event data on ARBs in hypertension, kidney disease, or the combination of ACE inhibition and AT_1 blockade which may theoretically preserve the benefits of the former, while adding the specificity of the latter. These are questions that presently remain unanswered.

Some of these issues are presently being evaluated in large multicenter trials with hard clinical endpoints. In the meantime, when considering an ARB for the treatment of hypertension, the clinician may find some guidance in a number of short-term studies that have compared the antihypertensive efficacy of several agents. These studies suggest that, while highly specific in their blockade of the AT-1 receptor, these agents may not all share the same blood pressure lowering properties. This finding may be explicable by some potentially significant pharmacological differences seen between these agents.

Comparisons between the ARBs: Clinical trials

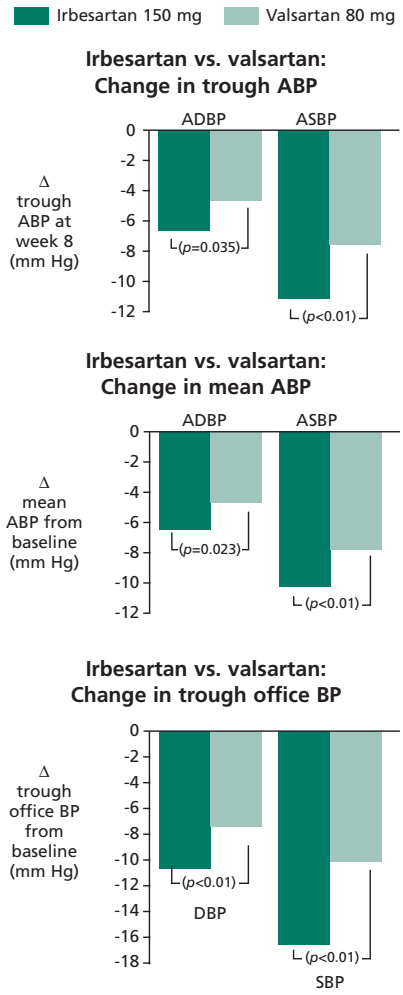
Losartan was the first AT-1 antagonist released and, consequently, most of the comparative studies with the newer agents have used it as a benchmark. Among others, irbesartan, valsartan, candesartan, and telmisartan have been evaluated in comparative studies against losartan. Irbesartan is, arguably, the AT-1 receptor antagonist that has been evaluated most extensively in comparative studies.

Recently, the first comparative study of irbesartan and valsartan employing 24-hour ambulatory blood pressure measurement (ABPM) was reported.[10] This was a randomized, multicenter, double-blind, parallel-group study designed to compare the antihypertensive efficacy of irbesartan 150 mg and valsartan 80 mg. The study enrolled male and female outpatients followed in specialty clinics or by their general practitioner for treatment of hypertension, aged 18-75 years, with an established history of mild-to-moderate hypertension (seated DBP between 95-110 mm Hg). A total of 45 sites participated in the trial. Patients were randomized to 8 weeks of double-blind treatment. ABPM, trough office BP (at 24±3 hours after the last dose of study medication) and self-measured BP (twice daily, morning and evening) were evaluated.

This is an important study as it is the first direct comparison of irbesartan with an ARB other than losartan. As well, the use of ABPM makes this study even more significant as it shows superiority of irbesartan over the entire 24-hour period and not just at trough as would be the case with the studies using office blood pressure. Greater blood pressure reduction over 24 hours may result in improved end-organ protection.

Irbesartan and valsartan produced significant BP reductions at 8 weeks. ABPM demonstrated greater BP reductions with irbesartan than valsartan for mean change from baseline in trough ADBP (-6.73 versus -4.84 mm Hg, respectively; p=0.035) and ASBP (-11.62 versus -7.50 mm Hg, respectively;

Figure 1: Comparison of the blood pressure lowering effects of irbesartan and valsartan by ambulatory and office BP measurements



p<0.01), and mean 24-hour ADBP (-6.38 versus -4.82 mm Hg, p=0.023) and ASBP (-10.24 vs. -7.76 mm Hg, p<0.01) (Figure 1). As well, irbesartan produced significantly greater reductions of office-measured trough DBP (-10.46 mm Hg for irbesartan versus -7.28 mm Hg for valsartan, p<0.01) and SBP (-16.23 versus -9.96 mm Hg, respectively; p<0.01). Similarly, irbesartan produced significantly greater reductions in self-measured SBP and DBP. Additionally, after 8 weeks of therapy, significantly more patients had their blood pressure normalized on irbesartan than valsartan (52.5% versus 38.2%; p=0.004) and there was a significantly greater proportion of responders for irbesartan than valsartan (63.9% versus 44.3%; p<0.01). Both of the drugs were well tolerated and the rates of

Table 1: Pharmacological comparisons among angiotensin II type 1 receptor blockers

Compound (active metabolite)	Active metabolite	Half-life, h	Bioavailability, %	Volume of distribution, L	Food effect	Daily dosing (mg)
Irbesartan	No	11-15	60-80	53-93	None	150-300
Losartan		2		34	Minimal	50-100
(EXP3174)	Yes	6-9	33	12		
Valsartan	No	5-9	23	17	Yes; ↓40%-50%	80-160
Candesartan	Prodrug	9	15	9	None	8-16
Telmisartan	No	24	42-58	500	Minimal; ↓6%	80
Eprosartan	No	5-9	13	NA	Yes; ↓25%	400-800

adverse events were low and not statistically different between the treatment groups.

The first study comparing irbesartan to losartan was a multicenter international study, including several Canadian sites, that compared the antihypertensive efficacy of the two agents.[11] In this double-blind, 8-week, placebo-controlled study, nearly 600 patients were randomized to 1 of 4 groups: losartan 100 mg once daily, irbesartan 150 mg or 300 mg daily, or placebo. At baseline, all 4 groups had equivalent seated systolic (SBP) and diastolic blood pressure (DBP), with a mean of 154/101 mm Hg. The blood pressure lowering effect of losartan 100 mg daily (the maximum recommended dose of this agent) was not different than the effect of irbesartan 150 mg, the recommended starting dose for this antagonist. In contrast, irbesartan 300 mg achieved significantly greater SBP and DBP reductions than losartan. At 8 weeks the differences were: -11.7 mm Hg for irbesartan versus -8.7 mm Hg for losartan in DBP reduction ($p<0.01$), and -16.4 mm Hg versus -11.3 mm Hg, respectively, for SBP reduction ($p<0.01$). These differences represent an advantage of irbesartan of 35% and 45%, respectively, for DBP and SBP reduction.

In contrast to the previous forced-titration study, a second study comparing irbesartan and losartan was performed with an elective titration design,[12] a design that is more consistent with the likely pattern of use in clinical practice. 432 patients with seated DBP of 95-115 mm Hg were randomized to receive irbesartan 150 mg daily or losartan 50 mg daily. The medications were titrated at week 4 to irbesartan 300 mg or losartan 100 mg if the trough seated DBP was still ≥90 mm Hg. The same parameter was used at week 8 to decide on the addition of hydrochlorothiazide. At week 8, the mean reduction in seated DBP was greater in the irbesartan monotherapy group by 2.3 mm Hg ($p<0.02$) and at week 12 by 3 mm Hg ($p<0.002$). The lowering of SBP was also significantly greater with the irbesartan-based therapy, achieving a reduction of 13.8 mm Hg compared to 10.8 mm Hg in the losartan regimen ($p<0.002$) at week 12. As well, the percentage of patients requiring the addition of hydrochlorothiazide was significantly lower in the irbesartan group compared to the losartan group.

Pharmacology of the ARBs

Within-class differences have emerged between the ARBs available in Canada that may have clinical implications.[13] A comparison of the pharmacological properties of the ARBs is provided in Table 1.[14] Although the clinical impact of an isolated difference in a pharmacokinetic parameter may be uncertain, a pharmacokinetic profile that shows multiple advantages is likely to impact the clinical efficacy and may explain the differences seen between the ARBs in the treatment of hypertension.

- Losartan must be metabolized to EXP 3174 to exert most of its clinically significant effects. Candesartan cilexetil is administered as a prodrug. Irbesartan, valsartan, telmisartan and eprosartan are, in contrast, administered as the active compounds.
- Although half-life is not the sole determinant of the duration of action of a drug, it is an important consideration in determining whether a drug can be administered on a once daily basis. Irbesartan and telmisartan have been shown to have the longest half-lives at 15 and 24 hours, respectively.
- In terms of bioavailability, irbesartan surpasses the other agents by a significant margin with only telmisartan being in a similar range.
- Although the clinical relevance of the volume of distribution of an ARB remains to be determined, it may correlate with the ability of a receptor antagonist to reach its target receptors at the tissue level. This could be of great significance given the increasing recognition of the role of the tissue RAS in disease. Irbesartan and telmisartan exhibit the largest volumes of distribution.
- There is no food effect on the absorption of irbesartan and candesartan; in contrast, varying degrees of food-related interference with absorption have been described with the other agents and it is somewhat more marked with valsartan. This effect of food on absorption has the potential of affecting

the clinical efficacy of the drug and introduces a potential element of inconvenience for the patient.

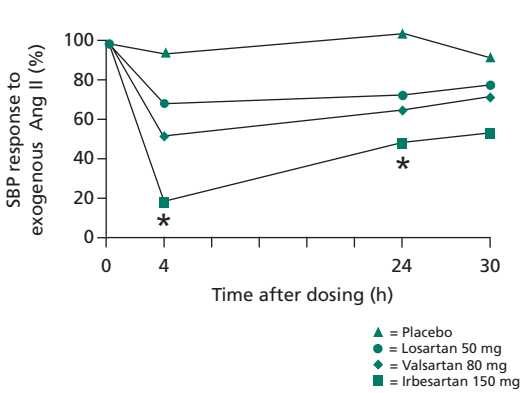
Comparisons between the ARBs: Basic studies

Given the potentially significant pharmacological differences described above, it is not surprising that a number of comparative studies have also found functional differences between the different agents of this class. The utilization of novel methodologies have yielded some rather interesting results. Recent studies have explored the angiotensin II antagonistic properties of irbesartan, valsartan, and losartan in humans by assessing the pressor responses to exogenous angiotensin II.

In the first study, the angiotensin II receptor blockade induced by the recommended starting dose of the three antagonists (losartan 50 mg, valsartan 80 mg, and irbesartan 150 mg) was evaluated in normal subjects.[15] In this randomized, placebo-controlled, double-blind study, subjects received a single dose of 1 of the 3 agents, and the study was repeated at weekly intervals until every subject had been tested with the 3 antagonists, as well as placebo. The blockade of the RAS was assessed by inhibition of the blood pressure response to exogenous angiotensin II at multiple time-points. Irbesartan blocked 88% of the angiotensin II-induced increase in systolic blood pressure compared with 51% for valsartan and 43% for losartan, ($p<0.01$ for the comparisons between drugs)(Figure 2). The effect of a single dose of the antagonists decreased over time and at 24 h, a residual effect was seen with the 3 drugs that was proportionately greater with irbesartan. In contrast, 30 hours after administration, only irbesartan induced a significant blockade versus placebo suggesting that the pharmacological differences between the ARBs may indeed impact their ability to antagonize angiotensin II *in vivo*.

In the second study, 18 healthy, normotensive male volunteers were randomized to receive irbesartan 150 mg, valsartan 80 mg, or losartan 50 mg in a double-blind, three-stage, crossover study. Vasopressor challenges with angiotensin II were performed before and after administration of the antagonists. The shift in the pressor response, measured as the increase in the diastolic blood pressure after administration of the drug, was utilized to calculate a dose ratio which represents the *in vivo* effect of the drug. For instance, a dose-ratio of 15, as seen with irbesartan at its peak action, means that a 15-fold higher amount of exogenous angiotensin II is necessary after the administration of the antagonist to achieve the same degree of blood pressure elevation as seen under control conditions. In this study, the three ARBs exhibited significant antagonistic effects to the angiotensin II challenge. However, the

Figure 2: Assessment of *in vivo* ARB blockade.



The time course of SBP response to the top dose of exogenous Ang II in the 4 phases. At 4 and 24 hrs, the blockade induced by irbesartan was significantly greater than that produced by losartan or valsartan. *P<0.05 vs valsartan and losartan.

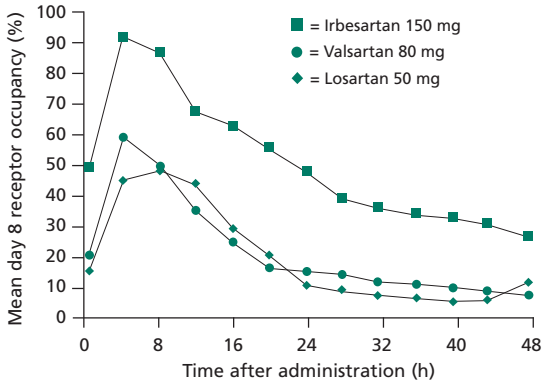
(Adapted from Mazzolai L, et al)[15]

response observed with irbesartan, in terms of the magnitude and duration of the antagonistic effect, was significantly greater than that with losartan or valsartan at all time points.

A different study assessed the comparative effects of the ARBs by a technique that measures *ex vivo/in vitro* angiotensin II antagonistic activity in plasma.[16] This technique – called a radioreceptor assay – utilizes purified lung AT-1 receptors to evaluate receptor occupancy *in vitro* by plasma obtained from the subjects following administration of an ARB. The ability of the human plasma samples to block angiotensin II binding to the purified receptors provides a measurement of the *in vivo* AT-1 antagonism in the individual from whom the plasma sample was obtained. All three drugs, at their usual starting doses, exhibited specific AT-1 antagonism. Receptor occupancy was, however, significantly higher with irbesartan than with either losartan or valsartan ($p<0.05$) (Figure 3). Indeed, administration of irbesartan resulted not only in much higher absolute levels of receptor occupancy, but also a significantly more sustained duration of action. The results of the vasopressor response and radioreceptor assays would be consistent with a superior clinical effect of irbesartan compared with the other two agents at doses employed commonly in clinical practice.

Caution must be exercised when extrapolating the results of studies in normotensive individuals into differences in long-term antihypertensive efficacy. However, the results of these studies do suggest that the

Figure 3: Angiotensin AT_1 receptor occupancy: Comparisons among ARBs.

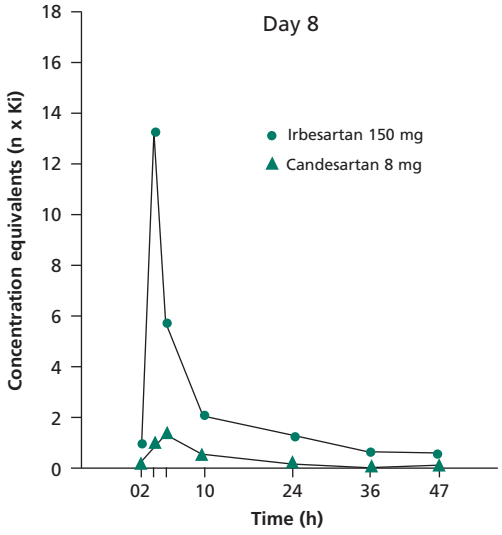


Irbesartan > losartan & valsartan
($p < 0.05$ at all time points)

In studies to assess the degree of receptor occupancy *in vitro*, all the 3 drugs demonstrated antagonistic effects, however, the percentage of receptor occupancy for irbesartan was significantly greater than either losartan or valsartan at all time points ($p < 0.05$).

(Adapted from Belz GG, et al)[16]

Figure 4: Extent and duration of angiotensin II antagonism



pharmacological differences between these agents could be clinically relevant.

Similar studies, comparing irbesartan with candesartan (150 mg versus 8 mg respectively), have been reported more recently. Compared to baseline values, resting DBP was lowered with both drugs, but irbesartan induced a slightly greater reduction ($p<0.045$). In this study, irbesartan and candesartan had equivalent angiotensin II antagonistic effects as demonstrated by identical dose-response ratios, the excess of angiotensin II needed to effect the same blood pressure response after the administration of the antagonist. This is likely a reflection of the strong degree of binding of the AT_1 receptor by both compounds. However, the *ex vivo/in vitro* radioreceptor assays demonstrated greater biologically active antagonistic concentration of irbesartan in the human plasma ($p<0.01$) and a more sustained duration of action (Figure 4).[17] As well, the investigators examined the response of plasma aldosterone levels following an infusion of exogenous angiotensin II before and after the administration of irbesartan or candesartan. Irbesartan produced a significantly greater blunting of plasma aldosterone levels than candesartan in response to angiotensin II.[18] This can be interpreted as demonstrating greater adrenal AT-1 antagonistic activity of irbesartan compared to candesartan. Additionally, irbesartan administration led to significantly higher plasma renin levels than candesartan ($p=0.02$). In view of the feedback mechanism that results in increased renin when the AT-1 receptor is blocked, these results could be interpreted as indicating greater biological efficacy of irbesartan at blocking the renal AT-1 receptor in the intact organism, although the clinical relevance of this finding is presently unknown.

Conclusion

The potent and highly specific antagonistic effect of the ARBs on the AT-1 receptor confers a significant potential to improve the current management of the most prevalent cardiovascular and renal diseases. These diseases, which include arterial hypertension, heart failure, as well as hypertensive and diabetic nephropathies, are associated with activation of the RAS at the tissue level. This chronic overreactivity of the local RAS system is perpetuated not only by ACE-mediated generation of angiotensin II, but also by alternate pathways that in some circumstances may account for the generation of most angiotensin II locally. This finding would suggest that the ARBs are a better, or at least more specific, way of antagonizing the RAS.

However, the large body of clinical experience with the ACE inhibitors is a powerful argument in support of the efficacy of this intervention. Recent studies suggest that the benefits of the ACE inhibitors are related significantly to their ability to prevent bradykinin degradation and to increase the biological activity of NO. However,

the ARBs are clearly superior in their tolerability profile as all members of this class, without exception, have been shown to have a placebo-like incidence of adverse effects. Ongoing trials are examining the potential benefits of ACE inhibitor and ARB combination which, theoretically, would preserve the enhancement of bradykinin while more completely, and specifically, antagonizing the effects of angiotensin II at the AT-1 receptor. As well, important trials are examining the effects of ARBs compared with other antihypertensive drugs on cardiovascular and renal end-points. An example of the latter is the Irbesartan Diabetic Nephropathy (IDNT) which is comparing irbesartan and amlodipine in over 1700 patients with type II diabetes, proteinuria and hypertension. In IDNT the end-points include doubling of serum creatinine, all-cause mortality and a composite of fatal and nonfatal cardiovascular events.

Although all of the available ARBs are highly specific in their antagonism of the AT-1 receptor, there are enough within-class pharmacological differences between these agents to lend support to the hypothesis that there may be significant differences in their clinical efficacy. A number of clinical and basic comparative studies have been reported. Most agents have been compared to losartan as it was the first antagonist released. Irbesartan has been utilized in a greater number and multiplicity of comparative study designs than any of the newer agents, from clinical trials to basic mechanistic studies, involving human subjects. In forced and elective titration studies, irbesartan has been shown to have greater blood pressure lowering effects than losartan. In a recent ABPM study, greater effects were seen with irbesartan than with valsartan over the entire 24-hour period. As well, recent reports have shown greater ability of irbesartan than candesartan to suppress the increase in plasma aldosterone induced by exogenous angiotensin II. This finding was correlated also with a slightly greater DBP reduction with irbesartan. Although the specific role of the ARBs will be established by an extensive program of ongoing trials, it would be reasonable for the clinician to factor the reported within-class differences into the selection process when deciding to prescribe one of these excellent agents.

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