

# Scientific Update™

## The Role of Irbesartan in Hypertension and Diabetic Kidney Disease

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Despite a multitude of antihypertensive therapies, hypertension remains a key problem for millions of Canadians at imminent risk for myocardial infarction (MI) and stroke. Canadian data indicate that as many as 40% of the population are unaware of their hypertension; furthermore, even among those with a diagnosis, only a fraction are achieving optimal control. The newest class of antihypertensive agents – the angiotensin II receptor blockers (ARBs) – may offer some unique advantages, particularly in view of their low adverse event/side effect profile. By blocking the AT<sub>1</sub> receptor, the ARBs provide a unique opportunity for inhibition of the renin-angiotensin system (RAS) which is known to play a crucial role in hypertension and target-organ damage. The following summary focuses upon the role of irbesartan in the management of hypertension and diabetic kidney disease.

### The Canadian Heart Health Survey

From 1986 to 1992, a survey of 23,000 Canadians aged 18-74 found that 22% had elevated blood pressure (BP) levels (systolic BP  $\geq$ 140 mm Hg and/or diastolic BP  $\geq$ 90 mm Hg).<sup>1</sup> This suggests that approximately 4.1 million Canadians have hypertension. Importantly, 42% of those with elevated BP were unaware of their hypertension, 19% were aware but not receiving treatment, 23% were being treated but were not under ideal control, leaving only 16% of all hypertensives being adequately treated (Figure 1).

### Medical therapy for hypertension

After identifying a patient with hypertension, the first step in management is employing lifestyle changes such as weight loss, smoking cessation, alcohol restriction, and encouragement for exercise. These measures can all have a profound impact on BP control and should be adopted together with a drug regimen that does not detract from a patient's quality of life.

Numerous classes of agents have been shown to be effective in lowering BP. However, even those drugs (eg, diuretics, beta-blockers) that impact on BP measurements and clinical outcomes in randomized, controlled trials are not always as effective as monotherapy and/or may not be tolerated by some patients. Additional or alternative therapies include calcium channel antagonists, angiotensin-converting enzyme (ACE) inhibitors, and ARBs. A handful of randomized trials have compared some of these classes to placebo and suggested that in selected settings (eg, isolated systolic hypertension), treatment with drugs other than diuretics or beta-blockers may be considered. While these groups of agents, particularly ARBs, appear to have a lower degree of side effects that could potentially lead to fewer patients discontinuing their antihypertensive therapy, there are either limited or no long-term clinical trial data to prove that mortality, MI, and stroke are indeed reduced as a consequence of these treatments.

Nonetheless, ARBs may ultimately play a key role, particularly in combination with other antihypertensive drugs, since up to 50% of all patients who receive antihypertensive therapy do not respond adequately to early generation therapies. Furthermore, not all antihypertensive classes appear to have the same impact on target end organ damage. For

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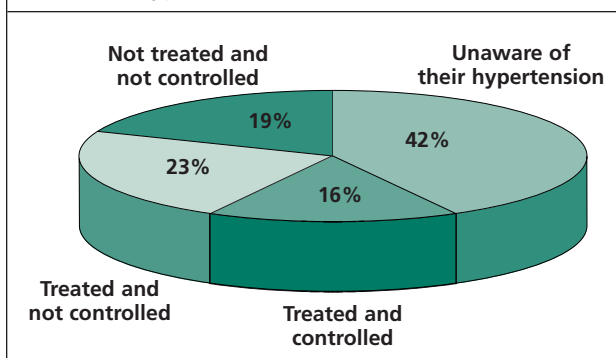
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**Figure 1: Awareness, treatment, and control of hypertension in Canada<sup>1</sup>**

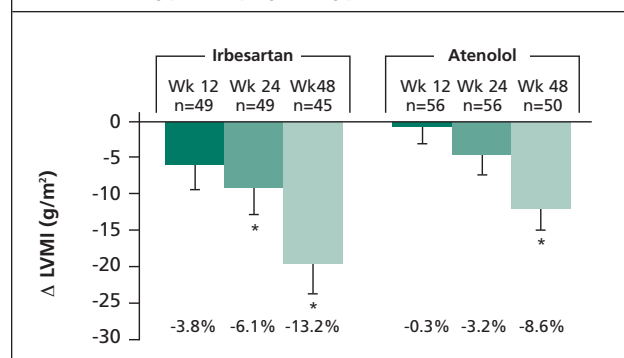


example, left ventricular hypertrophy (LVH), an important independent risk factor for total mortality and for cardiovascular morbidity and mortality, appears to be reduced to a greater extent by agents that impact on the RAS (eg, ACE inhibitors and ARBs). While no studies have confirmed that LVH reduction (beyond that achieved with adequate BP lowering) translates into reduced mortality, hypertensive patients with established LVH are clearly at higher risk for long-term complications. For example, Kahan et al<sup>2</sup> randomized 115 hypertensive patients (mean age 54 years, 68% male) with echocardiographically-documented LVH to either the ARB irbesartan (150 mg titrated to 300 mg) or the beta-blocker atenolol (50 mg titrated to 100 mg). In patients with seated diastolic BP  $\geq 90$  mm Hg, low-dose hydrochlorothiazide (12.5 mg titrated to 25 mg) or the dihydropyridine calcium blocker felodipine (5 mg titrated to 10 mg) was added. Repeat echocardiograms were performed at 3, 6, and 12 months. While both therapies reduced BP, irbesartan had an apparently more rapid reduction in left ventricular mass (Figure 2). In addition, there was less fatigue (7% vs 26%) and bradycardia (0% vs 26%) in irbesartan-treated patients.

### Blood pressure control: A review of irbesartan

Irbesartan, marketed jointly by Bristol-Myers Squibb and Sanofi, is a potent, long-acting, orally active ARB. Results of 8 multicentre, randomized, placebo-controlled, double-blind, parallel-group studies were pooled to assess the efficacy of irbesartan over the dose range of 1-900 mg.<sup>3</sup> A total of 2,955 adults with a seated diastolic BP of 95-110 mm Hg were randomized to treatment with oral irbesartan once daily or placebo for 6-8 weeks. Demographic characteristics (mean BP 151/101 mm Hg; mean age 54 years; 63% male; 82% white) were similar across all dose groups. After the groups were pooled, antihypertensive efficacy was assessed by therapeutic response (trough seated diastolic BP < 90 mm Hg or a reduction from baseline of  $\geq 10$  mm Hg) and by modelling of the maximum reductions in trough and peak seated systolic and diastolic BP. Antihypertensive effects increased with

**Figure 2: Reduction of left ventricular hypertrophy in hypertension**



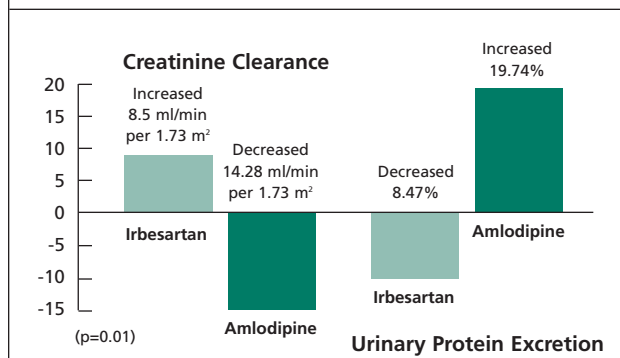
increasing doses and reached a plateau at  $\geq 300$  mg. Irbesartan 150 mg provided placebo-subtracted reductions in trough seated systolic and diastolic BP of approximately 8 and 5 mm of Hg, respectively, with 56% of patients displaying a favourable response. In conclusion, irbesartan provided clinically significant BP lowering with a clear relationship between (log) dose and antihypertensive effect.

In direct comparative studies of irbesartan and other antihypertensive agents, hypertensive control with irbesartan has also been favourable. For example, Mimran et al<sup>4</sup> performed a multinational, 51 site, double-blind, randomized study evaluating the full-dose range of the ACE inhibitor enalapril (maximum 40 mg daily) and irbesartan (maximum 300 mg daily) in patients with mild to moderate hypertension (seated diastolic BP 95-100 mm Hg). Irbesartan was as effective as the full dose range of enalapril in lowering BP with a trend towards a lower incidence of adverse effects, especially cough.

Larochelle et al<sup>5</sup> also performed a multicentre, randomized, double-blind study comparing the two agents in patients with more severe hypertension (seated diastolic BP 115-130 mm Hg). Patients received once daily doses of irbesartan (150 mg titrated to 300 mg) or enalapril (20 mg titrated to 40 mg), respectively. Open-label adjunctive therapy (hydrochlorothiazide, atenolol, and nifedipine) could be added after week 4 if BP control remained inadequate. Again, there was similar efficacy seen with both agents in BP-lowering, but the incidence of side-effects was lower in the irbesartan group; specifically, cough was much less frequent (2.5% vs 13.1%,  $p=0.007$ ).

Pohl et al<sup>6</sup> compared the safety and efficacy of irbesartan and the calcium channel antagonist amlodipine in hypertensive patients with type II diabetic nephropathy. In this double-blind, active-controlled pilot study, 47 patients (seated systolic BP 140-185 mm Hg or diastolic BP 90-110 mm Hg or treatment for hypertension) were randomized to receive either irbesartan (75 mg titrated to 300 mg) or amlodipine (2.5 mg titrated to 10 mg) over 12 weeks. Both therapies were effective

**Figure 3: Creatinine clearance and urinary protein excretion rates in patients receiving amlodipine and irbesartan<sup>6</sup>**



in reducing systolic and diastolic BP; however, marked differences in renal function were apparent. For example, there was a statistically significant worsening in creatinine clearance (Figure 3) among amlodipine-treated patients, while those receiving irbesartan had an improvement (-14.3% vs 8.6%,  $p < 0.01$ ). This was associated with a non-significant, but interesting difference in proteinuria; in the irbesartan group proteinuria decreased by 8.5%, while in the amlodipine group it increased by 19.7% ( $p = 0.23$ ). Adverse events/side effects were reported by a greater percentage of patients treated with amlodipine compared with irbesartan.

In another pilot study, 20 patients with mild-to-moderate hypertension were randomized to a double-blind, cross-over comparison of irbesartan (100 mg/day, a sub-therapeutic dose) versus enalapril (20 mg/day). Renal hemodynamics were determined on the first day of drug administration and 12 and 24 hours after the last dose during 6-week treatment. Both agents lowered mean ambulatory blood pressure effectively. Further, both agents induced a renal vasodilatation without a significant change in glomerular filtration rate. However, the time course appeared to differ: irbesartan had no significant acute effect 4 hours after the first dose, but after 6 weeks of therapy a renal vasodilatory response was found 12 and 24 hours post-dose. Enalapril was effective acutely and 12 hours after administration, but no residual effect was found 24 hours post-dose. This suggests that the impact of irbesartan on renal vasodilatation may be favourable for a longer duration.<sup>7</sup>

Results of these small studies have led to the initiation of the Irbesartan Diabetic Nephropathy Trial (IDNT) which will compare the effects of irbesartan, amlodipine, and usual care (placebo) on renal function, morbidity, and mortality in hypertensive patients with type II diabetes and diabetic nephropathy. The hope is that irbesartan can slow the rate of progression of renal disease in this high-risk population. This study will include 1,750 patients in more than 200 sites worldwide, with a minimum follow-up of 2 (average 3) years, and the anticipated study results in the year 2001. In

addition, the IRbesartan MicroAlbuminuria type II (IRMA II) diabetes mellitus in hypertensive patients study will compare the effects of irbesartan (150 mg or 300 mg) and usual care (placebo) on the progression of incipient to overt nephropathy and examine changes in renal function in hypertensive patients with type II diabetes and microalbuminuria. This study will include 550 patients in more than 110 sites worldwide with an average two-year follow up and anticipated study results at the end of 2000.

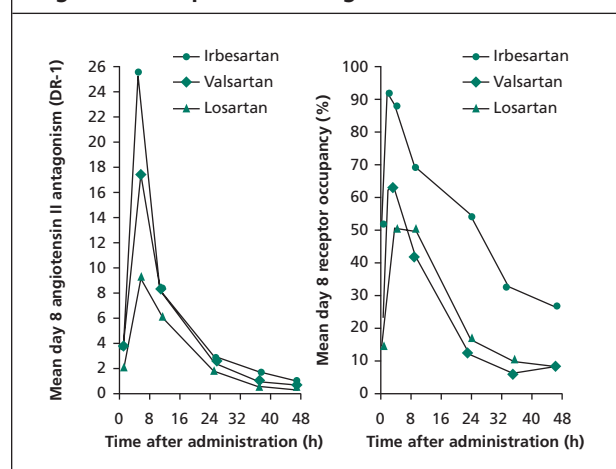
### Differences between the ARBs

There are some data indicating potential differences between various ARBs. Mazzolai et al<sup>8</sup> evaluated blockade of the RAS in normotensive subjects in a double-blind, placebo-controlled, randomized four-way crossover study. At one week intervals, 12 subjects received a single dose of losartan (50 mg), valsartan (80 mg), irbesartan (150 mg) or placebo. Blockade of the RAS was assessed before and 4, 24, and 30 hours after drug intake by three independent methods:

- (1) inhibition of the BP response to exogenous angiotensin II (ang II);
- (2) *in vitro* ang II receptor assay;
- (3) reactive changes in plasma ang II levels.

At 4 hours, losartan blocked 43% of the ang II-induced systolic BP increase; valsartan, 51%; and irbesartan, 88%, respectively ( $p < 0.01$  between drugs). The effect of each drug declined with time. At 24 hours, a residual effect was found with all three drugs, but at 30 hours, only irbesartan induced a marked, significant blockade as compared to placebo. Similar results were obtained when ang II receptor blockade was assessed with an *in vitro* receptor assay and by the reactive rise in plasma ang II levels. Thus, this study suggests that the first administration of the recommended starting dose of irbesartan induced a greater and longer lasting ang II receptor blockade than that of the other ARBs, valsartan, and losartan in normotensive subjects.

**Figure 4: Comparison of angiotensin II inhibition**



Belz et al<sup>9</sup> also compared irbesartan (150 mg), valsartan (80 mg), and losartan (50 mg) in 18 healthy males in a double-blind, randomized, crossover-designed study. Ang II dose-effect curves of diastolic BP and radioreceptor assay were obtained before and up to 47 hours after single and multiple doses of the ARBs. While all of the ARBs clearly demonstrated antagonistic effects to ang II, there was a greater extent and longer duration of the inhibitory effect of irbesartan (Figure 4). Further, the apparent half-lives of the decay of the antagonistic effects were 8 hours for valsartan and losartan, whereas it was 15-18 hours with irbesartan. Thus, in these normal volunteers receiving the recommended initial doses of the three ARBs, irbesartan demonstrated the slowest decay and longest duration of ang II antagonism. Whether these interesting findings translate into clinical differences remains unknown. However, it does raise the hypothesis that the apparently stronger and longer lasting antagonistic activity of irbesartan may provide greater than 24 hour benefit and this may be relevant in patients who are intermittently compliant and tend to miss their daily dose.

#### Other studies

There have also been a number of comparative trials of the ARBs that also support the concept of differences between agents within the ARB class.

- In a study by Andersson et al<sup>10</sup> in patients with mild to moderate hypertension, the effect on trough diastolic BP was significantly, more pronounced for candesartan 16 mg daily compared to losartan 50 mg daily. Candesartan 8 mg daily was equal to losartan 50 mg daily, and losartan 100 mg daily was not examined.

- In a study by Kassler-Taub et al,<sup>11</sup> 567 patients were randomized to once daily therapy with placebo, 100 mg losartan, 150 mg irbesartan, or 300 mg irbesartan for 8 weeks. Reductions from baseline in trough seated diastolic BP and trough seated systolic BP with 300 mg irbesartan were greater than with 100 mg losartan. Throughout the study, the antihypertensive effect of 150 mg irbesartan was the same as that of 100 mg losartan.

- Oparil et al<sup>12</sup> found that irbesartan 150-300 mg daily ± hydrochlorothiazide had a significantly, greater BP lowering effect than losartan 50-100 mg daily ± hydrochlorothiazide after 12 weeks treatment in a study of 370 patients with mild-to-moderate hypertension.

- In a study by Hedner et al<sup>13</sup> in 1,369 patients with mild to moderate hypertension, valsartan 80/160 mg was as well tolerated and as effective as losartan 50/100 mg in lowering mean seated diastolic and systolic BP; valsartan 160 mg had a significantly higher responder rate than losartan 100 mg.

Some direct comparisons have still not been performed (eg, candesartan vs. irbesartan) and one should be extremely cautious about reaching inferential conclusions from the comparison of the different trials mentioned above. The

American Food and Drug Administration recently concluded that no significant differences between ARBs (in terms of BP lowering efficacy) could be confirmed at present based on a meta-analysis, adjusting for differences between studies.

#### Conclusion

The unique action of the ARBs on the RAS provides this therapeutic class with the potential, but still unproven, ability to overcome some of the limitations inherent to other classes now used for the treatment of hypertension. In particular, the comparable BP lowering effects with similar or even greater tolerability than other antihypertensives may ultimately lead to greater “first-line” use of ARBs in the treatment of hypertension and target end-organ damage. The results of large ongoing clinical trials will help to further clarify the precise role that ARBs will play in the future management of our patients.

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