SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

Cardioprotection and Renin-angiotensin System Blockade

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Angiotensin-II antagonists are the newest form of medical management of hypertension. Compared to other antihypertensive drugs, angiotensin-II receptor blockers may provide more complete inhibition of the renin-angiotensin system, which is known to contribute to the pathogenesis of hypertension and heart failure. As a class, angiotensin-II blockers have favorable pharmacokinetics, antihypertensive action, and side-effect profiles. Irbesartan will soon be the newest angiotensin-II antagonist available to Canadians.

Hypertension: The global burden of disease

The Global Burden of Disease Study is an international collaborative effort to assess risk factors for morbidity and mortality around the world. This study shows that cardiovascular disease (CVD) in general, and hypertension in particular, account for a significant proportion of the death and disability reported internationally.[1] Hypertension is the third leading cause of death, following malnutrition and tobacco use (see figure 1), and accounts for 1.4% of the total disease and injury burden as estimated by Disability-Adjusted Life Years (DALYs), a measure that encompasses years of life lost due to premature mortality and years lived with disability.

Awareness, treatment, and control of hypertension

Epidemiologic studies suggest that despite an increased awareness of hypertension, not all patients receive treatment, and that even among those who do, adequate control is infrequently achieved. For example, estimates based on the Third National Health and Nutrition Examination Survey (NHANES III)[2] imply that 43 million adults in the U.S. (24% of the adult population) have hypertension. Of these hypertensive individuals, approximately 70% are aware of their disease, 50% are being treated with antihypertensive medication, and only 24% are considered to be controlled with a systolic blood pressure <140 mm Hg and/or a diastolic pressure <90 mm Hg.

Efficient management of patients with hypertension is obviously affected by patients' premature discontinuation of therapy. Side effects, tolerability issues, and over-all dissatisfaction with medication can affect compliance, which in turn influences the outcomes of antihypertensive therapy. Traditional antihypertensive therapies, including diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium-channel blockers (CCBs), each have unique side-effect profiles that can limit treatment and compliance and hence their over-all effectiveness.

While progressive increases in the dose of antihypertensive therapies often leads to increased efficacy, all agents have a "plateau" phase of effectiveness. At the same time, increasing the dose leads to an increasing number of side effects, and thus physicians and patients often accept sub-optimal efficacy in order to minimize significant adverse events (see figure 2).

Angiotensin-II receptor blockade

The newest class of antihypertensive agents is the angiotensin-II receptor blockers. Angiotensin-II (A-II) is a major component of the renin-angiotensin system (RAS), which is important in the pathophysiology of essential hypertension (see figure 3). The RAS consists of a cascade of enzymatic reactions that act on angiotensinogen and angiotensin-I (A-I), leading to the formation of A-II, a potent

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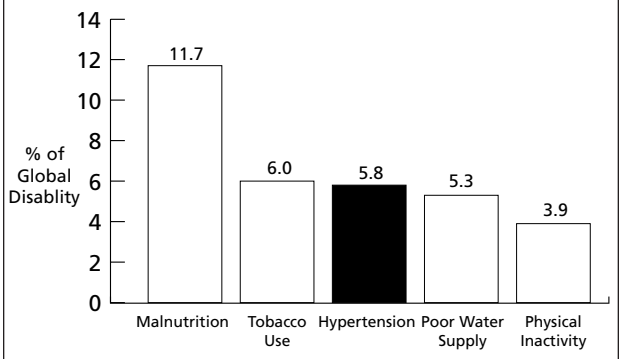
Figure 1: Global Burden of Disease Study – proportion of deaths attributable to leading risk factors.

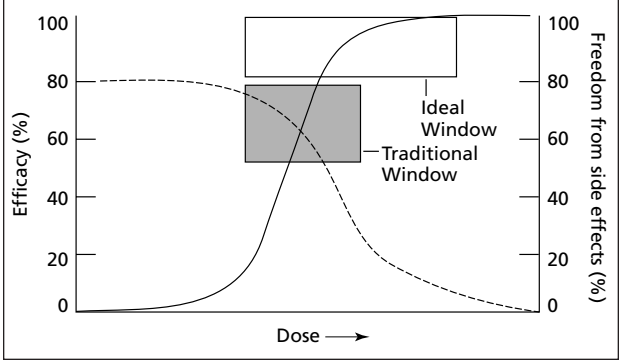


adapted from Murray and Lopez[1]

vasoconstrictor. A-II is produced through the hydrolysis of A-I by ACE, an enzyme that also inactivates bradykinin. The AT_1 receptor mediates the actions of A-II that result in vasoconstriction, increased blood volume, and cardiac and vascular remodeling, each of which contributes to increased blood pressure.

While ACE inhibition is clearly a mechanism within the RAS that blocks formation of A-II, inhibition at the site is not optimal due to the existence of other pathways through which A-II can be formed. Angiotensinogen can be converted to A-II through non-renin enzymes. In contrast, A-II inhibitors block the action of A-II at the final step of the pathway, directly at the AT_1 receptor site; thus, unlike ACE inhibitors, they do not interfere with enzymatic processes within the RAS. In addition, the A-II receptor blockers do not potentiate bradykinin, which is thought to contribute to the development of cough and angioedema associated with ACE inhibitors.

Figure 2: Ideal vs traditional therapeutic window of antihypertensive agents.



Pharmacokinetics of A-II antagonists

Several A-II antagonists are in various stages of development, including losartan (currently available), irbesartan (soon to be available), valsartan (soon to be available), candesartan, tasosartan, and eprosartan. Bioavailability and plasma half-lives vary substantially among these compounds. Irbesartan has the greatest bioavailability (60–80%) and the longest half-life (approximately 11–15 hours). Losartan and candesartan require biotransformation to a more potent active metabolite for their antihypertensive effects, but irbesartan and valsartan have direct effects with a lower percentage of protein binding.

Clinical experience with irbesartan

Irbesartan pharmacokinetic parameters are predictable and linear over the therapeutic dose range. No clinically important accumulation of irbesartan occurs with repeated dosing (steady state) compared with single dosing (single dose). The pharmacokinetic parameters of irbesartan were clinically similar regardless of age and sex according to a small study of healthy subjects.[3] Although irbesartan is metabolized in the liver and excreted by the hepatic and renal routes, patients with renal[4] and hepatic[5] impairment did not require dose adjustments.

Several studies have shown significant reductions in systolic and diastolic blood pressures with once-daily administration of irbesartan as compared to placebo.[6,7] In addition, the antihypertensive effects of irbesartan have been compared with those of other antihypertensive agents in randomized, double-blind studies; these studies suggest that 75–150 mg of irbesartan is comparable in its blood-pressure-lowering effects to 50–100 mg of atenolol,[8] and 75–300 mg of irbesartan is comparable to 10–40 mg of enalapril.[9] In 159 patients with more severe hypertension (diastolic BP 115–130 mm Hg), a 12-week randomized double-blind study of irbesartan and enalapril showed similar blood-pressure-lowering efficacy but more rapid normalization of BP with irbesartan.[10]

Safety and tolerability

All angiotensin-II antagonists have an excellent side-effect profile. Data pooled from all patients (n=2,606) in placebo-controlled studies of irbesartan monotherapy demonstrate that the frequency of adverse events experienced during the first day of treatment and over weeks to months of therapy was comparable to that seen with placebo. In particular, the overall incidence of hypotension and its symptomatic equivalents (e.g., dizziness) was less than 5%, similar to placebo.

Regression of left ventricular hypertrophy

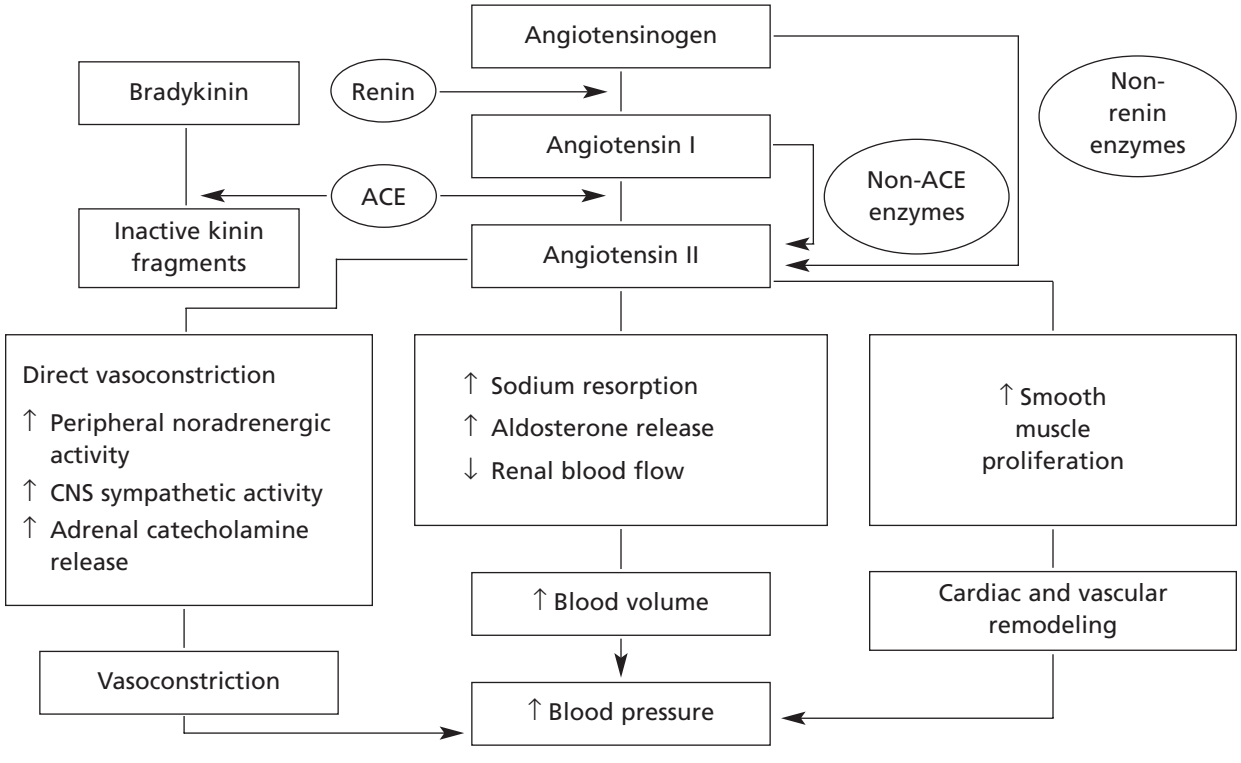
Left ventricular hypertrophy (LVH) is an important manifestation of end-organ damage, and it results from trophic changes influenced by factors such as increased levels of plasma norepinephrine, renin, and angiotensin-II. Several studies of hypertensives have shown higher mortality in those with LVH. A recent study elaborates on this.[11] The double blind, 48-week study involved 115 patients with mild-to-moderate hypertension (diastolic BP persistently >90 mm Hg) and evidence of LVH (LV mass index >131 g/m^3 in men and >100 g/m^3 in women). All patients were taking either hydrochlorothiazide or felodipine; to this they added either irbesartan (150 mg) or atenolol (50 mg). Both groups experienced similar blood-pressure reductions, but the irbesartan arm had an earlier and greater degree of LVH regression. At week 24, irbesartan reduced LV mass by 10.7 g/m^3 with atenolol reducing LV mass by 3.9 g/m^3. At week 48, irbesartan reduced LV mass by 19.7 g/m^3, atenolol by 10.9 g/m^3 – representing approximately a 40% difference at 48 weeks. In addition, 67% in the atenolol group and 34% in the irbesartan group reported adverse effects, suggesting superior tolerability and end-organ protection with irbesartan.

Angiotensin-II blockade in heart failure

A recent randomized trial (ELITE I) of losartan as compared to captopril for patients over 65 years of age with heart failure demonstrated a similar rate of hyperkalemia and drug-induced renal impairment, but there was a significantly lower incidence of cough and mortality (mainly due to a reduction in sudden death) in the losartan-treated group.[12] As the number of events, including death, was small, and the study was not designed to demonstrate a difference in clinical outcome, a larger study comparing these agents has been initiated (ELITE II).

Results of pilot studies examining the hemodynamic and clinical effects of irbesartan and heart failure have been presented in abstract form. They suggest superior benefits in irbesartan-treated patients—including improvement in LV ejection fraction—as compared to placebo, with or without concomitant ACE-inhibitor therapy. In a study of 134 patients with symptomatic heart failure and LV dysfunction (ejection fraction <40%), the tolerability profiles of irbesartan and lisinopril were comparable, including the incidence of worsening heart failure and serious adverse events.

Figure 3: Role of the renin-angiotensin system in the pathogenesis of hypertension.



While these and other studies of patients with heart failure have been encouraging, the large body of evidence supporting the use of ACE inhibitors in left ventricular dysfunction with or without heart failure means that we must await larger-scale, confirmatory trials before utilizing A-II receptor blockers instead of, or in addition to, ACE inhibitors.

Comparisons of A-II receptor blockers

Two studies have compared directly the efficacy of angiotensin-II blockers. In a double-blind study of 1,369 patients with mild-to-moderate hypertension, there was no significant difference between valsartan (80–160 mg) and losartan (50–100 mg) in lowering systolic and diastolic pressures after four and eight weeks of therapy; both agents were superior to placebo.[13]

Another study of 532 mild-to-moderate hypertensives compared irbesartan, losartan, and placebo over 8 weeks of therapy. Patients receiving 150 mg of irbesartan or 100 mg of losartan had comparable systolic and diastolic pressure reductions (9–11 mm Hg as compared to baseline); both agents were superior to placebo. However, patients receiving 300 mg of irbesartan had significantly greater lowering of systolic and diastolic BPs (12–16 mm Hg or an approximate 25% reduction, $p < 0.05$) as compared with those taking 100 mg of losartan [unpublished data]. This difference was statistically significant at the first week of therapy and continued to the end of the trial.

Summary

Angiotensins contribute to the pathogenesis of hypertension, arterial disease, cardiac hypertrophy, heart failure, and diabetic renal disease.[14] The efficacy of ACE inhibitors in some cardiovascular and renal diseases has encouraged the development of other drugs to inhibit the renin-angiotensin system. The newest of these are specific antagonists of angiotensin-II receptors. This group of agents, including irbesartan, appears to offer blood-pressure-lowering efficacy at least comparable to that of other well-established agents (diuretics, beta-blockers, ACE inhibitors) and a side-effect profile similar to that of placebo. The role of angiotensin-II antagonists in the treatment of heart failure (alone or in addition to ACE inhibition) appears favourable but requires further large-scale studies.

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