There has been a rapid growth in members of this new class of drugs; at the present time four are being actively marketed in Canada: Losartan (Cozaar®), valsartan (Diovan®), irbesartan (Avapro®), candesartan (Atacand®).

**Indications:** Hypertension is at present the only approved indication for these drugs in Canada.

**Mechanism of Action:** The final active messenger of the renin-angiotensin pathway is angiotensin II. Angiotensin II binds to AT$_1$ receptors to cause vasoconstriction and fluid retention, both of which lead to an increase in blood pressure. The angiotensin II receptor blockers lower blood pressure by blocking the AT$_1$ receptors. Therefore they have similar effects to angiotensin converting enzyme (ACE) inhibitors, which inhibit the synthesis of angiotensin II by ACE (see illustration). However, non-ACE pathways can produce some angiotensin II. ACE inhibitors also decrease bradykinin breakdown and this action could be involved in some of the beneficial and adverse effects of that class of drugs. Therefore, a potential for differential clinical effects exists for these two classes of drugs.

**Pharmacokinetics:** The four drugs differ in how they are handled in the body (see Table).

**Evidence in hypertension:** Angiotensin receptor blockers have not been studied in any randomised controlled trials (RCTs) measuring long-term health outcomes in patients with hypertension. ACE inhibitors have likewise not been compared to placebo in this clinical setting. Two recent RCTs have demonstrated that captopril is associated with similar total cardiovascular events as compared to thiazides and/or beta blockers (10,985 hypertensive patients) and as compared to atenolol (1,148 hypertensive patients) with type 2 diabetes. In 3 RCTs involving patients with hypertension and diabetes and hypertension, ACE inhibitors were associated with significantly fewer cardiovascular events than dihydropyridine calcium channel blockers (CCBs). Most likely these 3 trials reflect worse outcomes with dihydropyridine CCBs, consistent with previous evidence (Letter 16).
There are 2 published RCTs demonstrating a significantly greater antihypertensive efficacy of irbesartan as compared to losartan.7,8 One published trial comparing 8 mg of candesartan with 50 mg losartan and one unpublished trial comparing 80 - 160 mg valsartan with 50 - 100 mg losartan showed no differences in blood pressure lowering efficacy.

**Evidence in Congestive Heart Failure:** There is one published RCT (722 patients in the ELITE trial) comparing losartan with captopril in patients over 65 with heart failure.10 The primary endpoint of the trial, persistent increase in creatinine, was the same in both groups (10.5%). The secondary endpoint, admissions with heart failure, was also the same in both groups (5.7%). There was an unexpected decrease in total mortality (p < 0.05), in the losartan group (4.8%) as compared to the captopril group (8.7%) (ARR = 3.9%, NNT = 26). A larger trial evaluating morbidity and mortality is required and is in progress.

**Adverse effects:** Adverse event rates for angiotensin receptor blockers were low and similar to placebo in the trials to date. In a meta-analysis of the comparative trials above, the incidence of dry cough was significantly lower with angiotensin receptor blockers, 1.0%, as compared to ACE inhibitors, 5.5%. Withdrawals due to adverse events were also significantly lower with angiotensin receptor blockers, 4.8%, than with ACE inhibitors, 7.9%. When patients with an ACE inhibitor cough were randomized to an angiotensin receptor blocker, a thiazide, or an ACE inhibitor, the cough resolved in 81%, 80% and 19%, of patients respectively.11,12 Rare serious adverse effects that have been reported with the clinical use of angiotensin receptor blockers include: hepatotoxicity, angioneurotic edema, and neuropsychiatric symptoms.

**Precautions:** As with ACE inhibitors, renal impairment is likely in susceptible individuals whose renal function depends on the renin angiotensin system: bilateral renal artery stenosis, renal artery stenosis in solitary kidney and severe congestive heart failure.

**Contraindications:** pregnancy.

**Dose and Cost:** See Table. The cost of all the available dosage forms in this class is similar. Halving tablets halves the cost (eg 4 mg candesartan). This is not possible for valsartan, which comes in capsules.

**Conclusions:** Angiotensin receptor blockers act to modulate the renin angiotensin pathway at a different site compared to ACE inhibitors. There is suggestive evidence that angiotensin receptor blockers may not be as good at lowering blood pressure as ACE inhibitors. Because they are not associated with the intractable dry cough seen in some patients taking ACE inhibitors, angiotensin receptor blockers are indicated in patients who require an ACE inhibitor (see Therapeutics Letter 8) but who cannot tolerate it due to drug-induced dry cough.