

CLINICAL ISSUES IN HYPERTENSION

Canadian Coalition for High Blood Pressure Prevention and Control
Coalition Canadienne pour la Prévention et le Contrôle de l'Hypertension Artérielle



Hypertension: Multidrug Combination Therapy

Although many studies have shown treatment of hypertension reduces cardiovascular events, the majority of patients with hypertension in Canada are not adequately treated. Many of these patients require two or more antihypertensive agents for treatment of the appropriate blood pressure goals, which can be achieved with minimal adverse effects.

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Control of hypertension reduces mortality and morbidity and provides end-organ protection. However, about two-thirds of patients with hypertension do not have adequate blood pressure control with monotherapy and, thus, require two or more agents to achieve blood pressure goals.¹ Multidrug therapy is necessary for most patients with hypertension.

How are individual agents selected for multidrug therapy?

The active mechanism of blood pressure-lowering drugs varies from agent to agent and can be additive when combined appropriately.

Angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers reduce peripheral resistance. Diuretics reduce cardiac output and decrease peripheral resistance. Beta blockers primarily decrease cardiac output and renin production. The appropriate combination of agents can be chosen on the basis of the pharmacologic actions of each drug (Table 1). For example, a vasodilator may decrease

peripheral resistance, leading to activation of the sympathetic nervous system, which can be decreased by a beta blocker. In patients taking an ACE inhibitor or an ARB, diuretics will activate the renin-angiotensin system and potentiate the effect of the ACE inhibitor. In specific patients, such as those with renal disease, greater benefit can be achieved with a combination of an ACE inhibitor and an ARB than with any other combination.²

About 2/3 of patients with hypertension do not have adequate BP control with monotherapy; they require 2 or more agents to achieve BP goals.



Combination Therapy

Table 1

Hypertensive agents for multidrug therapy

Agents	Effect
ARBs ACE inhibitors Calcium channel blockers	Reduce peripheral resistance
Diuretics	Reduce cardiac output and decrease peripheral resistance
Beta blockers	Primarily decrease cardiac output and renin production

ARB: Angiotensin II receptor blocker
ACE: Angiotensin-converting enzyme

What is the clinical use of multidrug combinations?

Unfortunately, combination therapy is used infrequently in the management of patients with hypertension. The current approach begins with lifestyle modifications and monotherapy. Although a single drug approach is ineffective in many patients, often the treatment regimen is not modified, leading to inadequate control of blood pressure. In the few patients whose treatment is modified, many are simply titrated to a

larger dose of the same agent or switched to another form of monotherapy. A more reasonable approach would be to proceed with multidrug combination therapy early in management.

Multidrug combination therapy is usually more effective than monotherapy in achieving the goal of lowering blood pressure. The combination of a diuretic with an ACE inhibitor or an ARB results in a greater responder rate with smaller doses of each agent, than is possible with larger doses of either agent alone. As well, patient compliance is often better because of fewer adverse effects due to lower doses of the individual drugs used.

ARBs, as a class of drugs, are extremely well tolerated and can be used in combination with other agents with minimal change in the frequency or adverse effects. Conversely, some combinations may actually increase the risk of adverse effects, as would be expected when combining a non-dihydropyridine calcium channel blocker with a beta blocker. This risk increase is due to the potential of significant bradycardia or atrioventricular conduction delay.

What do the studies say?

Lowering blood pressure to specific goals in hypertensive patients has been well established in clinical trials, with the benefit of preventing stroke and coronary heart disease deaths. As well, specific blood pressure-lowering agents, such as ARBs, may provide added benefits, including end-organ protection.

The following clinical studies have shown important results:

- In the Reduction of End points in Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (**RENAAL**) study, losartan (and ARB) protected renal function to a greater degree than a comparable therapy with

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similar blood pressure reduction in patients with Type 2 diabetes and existing nephropathy.³

- In the Irbesartan in Diabetic Nephropathy Trial (**IDNT**), irbesartan (an ARB) similarly provided renal protection independent of lowering blood pressure as compared to other antihypertensive agents, in patients with type II diabetes and nephropathy.
- In the Losartan Intervention For End point reduction in hypertension (**LIFE**) study, losartan resulted in greater reduction of stroke and cardiovascular events as compared to treatment with a beta blocker and similar blood pressure reduction.⁴

What's the message?

Combination multidrug therapy usually provides greater success at lowering blood pressure and provides a better side-effect profile with smaller drug doses than is possible with monotherapy.

Combinations need to be selected on the basis of the active pharmacologic mechanisms and consideration must be given to patient characteristics, such as diabetes or nephropathy, and to the severity of hypertension.

Specific drugs for combination therapy need to be selected on the basis of the active mechanism and side-effect profile of the individual drugs, and then titrated as necessary to achieve the desired antihypertensive effect.

Then, the successful regimen can frequently be modified by switching to combination drug tablets for greater patient convenience and improved compliance. *Read*

References

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These studies show that combination therapy including an ARB may be very appropriate in specific patients, such as those with Type 2 diabetes and nephropathy.

High-risk patients, such as patients with diabetes or renal disease, have lower blood pressure goals and usually require multidrug approaches. These high-risk patients, and patients with severe hypertension, should be started on multidrug therapy as a first-line approach.