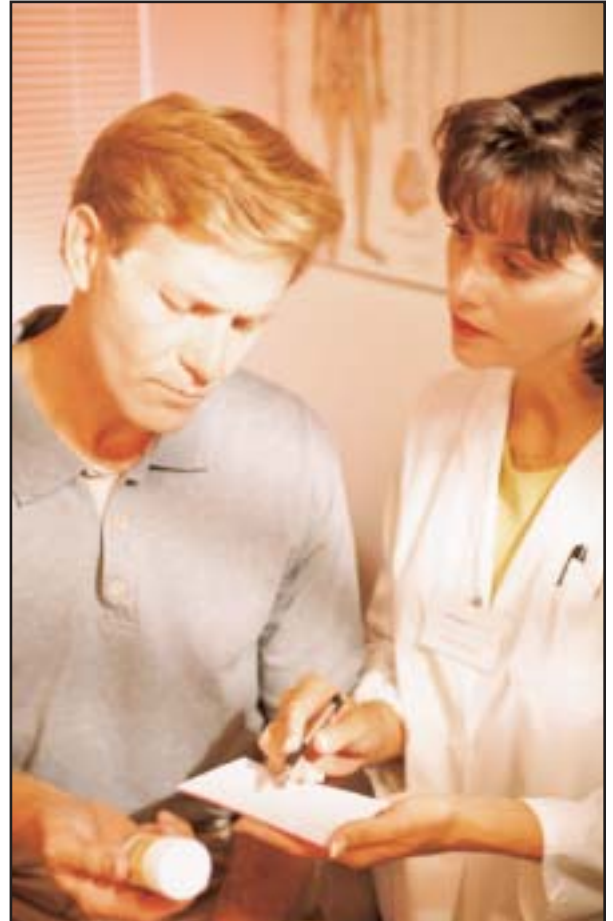


# COMBINATION THERAPY IN HYPERTENSIVE PATIENTS

The likelihood of lowering blood pressure to target could increase by using combination drug therapy to treat patients with hypertension.



By Ellen D. Burgess MD, FACP, FRCPC

Canada's Heart Health Survey showed that only 16% of hypertensive people in Canada are on medication and have their blood pressure under control.<sup>1</sup> In general, women are more likely than men to have their blood pressure (BP) controlled, and the systolic blood pressure (SBP) is more likely to be above target than the diastolic pressure (DBP). The one demographic group that had a larger proportion of controlled hypertensive patients was young women — approximately one-third of them are controlled.

Interestingly, this group also had the highest proportion of individuals following non-drug or lifestyle recommendations for hypertension control in addition to taking medication.

Generally, less than one-third of hypertensive patients control their BP with a single antihypertensive medication; the majority will require two medications, and some may require three or more. With lower target blood pressures (Table 1), the need for combinations of antihypertensive agents increases.

The main obstacle preventing our patients from reaching their target BPs is physician attitude. Physicians accept high BPs and either do not initiate drug therapy or do not increase the dose of a single medication or add a second one. In the majority of patients, combination therapy is ultimately required in order to lower the BP to target.

## About the author ...



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## ♥ Practical Point

Lifestyle modifications that can augment drug responsiveness in hypertensive patients include:

- ♥ **A reduced sodium diet** (80-110 mmol a day);
- ♥ **Reduced alcohol intake** (2 servings a day);\*
- ♥ **Weight loss** (4.5 kg or 10 lbs); and
- ♥ **Moderately vigorous exercise** (50-60 min/day, 3-4 days a week).

\* a serving of alcohol is 5 oz of wine, 1.5 oz of hard liquor or 12 oz of beer.

Table 1

### Target Blood Pressures

Essential hypertension	< 140/90
Diabetes mellitus	< 130/80
Renal disease	< 130/80
Renal disease with > 1 gm proteinuria	< 125/75

## Which Patients Are Considered High Risk?

Although the risk of having a cardiovascular event increases with increasing SBP, a patient's risk status is not defined solely by their BP. The classification of hypertension has been changed from "mild-moderate-severe" to "Stage 1, Stage 2, Stage 3" in order to assist health-care professionals in understanding that other factors are important in defining risk status.<sup>2</sup>

As seen in Table 2, the addition of diabetes alone, regardless of the level of elevated BP, increases the risk status of a

patient to the same as that of a patient who has already had a cardio/cerebrovascular event.

Other traditional risk factors, such as obesity, do not carry the same risk level as diabetes, and hence a patient must have two other risk factors to "equal" the elevation in risk caused by diabetes.

## Physiologic and Pharmacodynamic Basis for Combination Therapy

A brief review of the physiologic and pharmacodynamic mechanisms of hypertension will provide a background to better understand the most appropriate combinations of antihypertensive drugs. On a very fundamental level, there are four basic physiologic contributors to hypertension:

- a) sodium abnormalities;
- b) the sympathetic nervous system (SNS);
- c) the renin-angiotensin-aldosterone system (RAAS); and
- d) local ionic and hormonal mechanisms.<sup>3</sup>

Antihypertensive medications can be related to these hypertensive mechanisms (Table 3).

**a) Sodium abnormalities** linked to hypertension are primarily abnormal transport mechanisms that can be augmented or corrected by various diuretics. These membrane transport systems work to maintain a normal concentration of sodium inside the cell. When these transport systems do not work properly, there is an increase in intracellular sodium concentration. This results in a change in the receptor binding of vasopressor hormones and an increase in intra-

## Case

Mr. AE, 46, used to work on the oil rigs. One year ago, he moved to the city. He physically felt he could not continue working “in the field.” Since then, he has worked at a car dealership. He has gained 25 pounds and no longer walks or exercises. He feels tired during the day, but sleeps about eight hours every night.

He is known to have had hypertension for about 10 years, taking medication periodically. He stops his medication when the prescription runs out or when he believes he has a side effect from it (although he admits that the complaint does not improve when the drug is stopped). He has been on various medications over the years. An echocardiogram done a year ago noted left ventricular hypertrophy (LVH).



On clinical examination:

- His BP is 180/114 in the sitting position, taken twice after a five-minute rest.
- Pulse rate is 88 bpm, with no irregularity.
- Fundoscopic exams show normal optic discs, arteriolar narrowing with A-V nicking, but no hemorrhages or exudates.
- Heart sounds are normal and there are no murmurs.
- No bruits are heard over major arteries.
- Lung fields are clear.
- ECG is unchanged from before and consistent with LVH.

**Question: What steps should be taken?**

See Case Discussion on page 39.

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## Combination Therapy in Hypertensive Patients

Table 2

### Risk Stratification of Hypertensive

Risk Factors	SBP	Stage 1 140-159	Stage 2 160-179	Stage 3 >180
	DBP	90-99	100-109	>110
0		Low	Medium	High
1 or 2		Medium	Medium	Very high
≥ 3 or TOD, diabetes		High	High	Very high
C/CV or renal disease		Very high	Very high	Very high

Risk stratification includes risk factors and the stage of hypertension.

- Low risk = the risk of a major cardiovascular event is < 15% over the next 10 years.
- Medium risk = 15% over the next 10 years.
- High risk = 20% to 30% over the next 10 years.
- Very high risk = > 30% over the next 10 years.

TOD = Target organ damage

SBP = Systolic blood pressure

C/CV = Cardio-cerebral vascular disease

DBP = Diastolic blood pressure

cellular calcium content; these changes result in an increase in the resting tone of the vascular smooth muscle cells and the response of the cells to the vasopressor hormones. Normalization of the intracellular sodium content by the diuretic(s) returns the tone and responsiveness of the vascular smooth muscle cells to normal. In the case of elderly persons or others with reduced kidney function, increased “volume” (increased extracellular sodium) may also contribute to hypertension. This too may be normalized with the use of diuretics. However, the use of diuretics may increase the activity of the RAAS.

**b) Abnormalities of the SNS** have been linked to primary hypertension as well as hypertension associated with alcohol excess, obesity and hyperinsulinemia. The increase in sympathetic nervous activity

leads to an elevated heart rate and cardiac output through a beta-adrenergic activity, whereas the increased peripheral vascular and increased sodium reabsorption by the kidney are mediated via alpha-adrenergic activity. The SNS is connected with the RAAS in such a way that they reinforce each other. Beta-adrenergic stimulation increases renal renin release and subsequent angiotensin II levels, whereas beta-adrenergic blockade will result in a modest reduction in renin.

**c) RAAS.** Angiotensin II and aldosterone have been linked to various aspects of hypertension and hypertensive complications including sodium reabsorption and vasoconstriction as well as glomerular, vascular and cardiac fibrosis. The use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers

(ARBs) is beneficial for patients with various hypertensive complications including congestive heart failure (CHF), left ventricular hypertrophy (LVH) and renal disease. These drugs also have a “cross-over” effect to modestly reduce the activity of the SNS.

**d) Local ionic and hormonal effects.** Increased BP has been shown to be associated with increases in intracellular calcium concentration. Accordingly, the use of calcium channel blockers (CCBs) results in a reduction in intracellular calcium content and lower BP. As a result of the decrease in intracellular calcium content, the vascular smooth muscle cells have a reduced response when stimulated by any vasoconstrictor hormone including norepinephrine and angiotensin II. This is why CCBs have been adopted widely for use in patients with essential or secondary hypertension.

## Dose-related Adverse Effects

Tolerability is an important issue for patients. An increased dose of antihypertensive medication is associated with improved BP lowering. The older medications (diuretics, beta blockers, clonidine, alpha-methyldopa) are also characterized by a similar association between increasing dose and adverse effects. This does not appear to be the case with most of the newer antihypertensive medications.

Although CCBs are plagued with increased side effects with higher doses, ACEIs and ARBs are not. As well, there are fewer side effects with the newer medications. Continued persistence of treatment is most likely if patients are prescribed ARBs.<sup>4</sup> Prior to the release of ARBs, ACEIs were the best tolerated antihypertensive medications.

Table 3

### Relating Drugs and

Drug Class	Pathophysiology Which the Drug Reverses
Diuretic	Sodium abnormalities
Beta blockers	Increased cardiac output, heart rate
Alpha blockers	Increased vascular resistance
ACEIs, ARBs	Increased RAAS activity
CCBs	Response to vasopressor agents

ACEI = ACE inhibitors, ARB = Angiotensin II receptor blockers  
 RAAS = Renin-angiotensin-aldosterone system  
 CCB = Calcium channel blocker

## Why We Haven't Used Combination Therapy in the Past

In the past, combination therapy was not generally recommended by the various groups that developed guidelines for the treatment of hypertension. Physicians were told to initiate therapy with a diuretic or beta blocker and increase the dose to maximum before adding, or substituting, a second drug. Following this old “stepped care” approach meant only a minority of patients moved on to two-drug therapy.

Unfortunately, patients would drop away from therapy because they developed adverse effects from the high doses of medications being used. As well, target BPs had not been validated and many physicians used 160/100 mmHg as their target BP. When fixed-dose combination tablets were introduced to the market, physicians reject-

## Combination Therapy in Hypertensive Patients

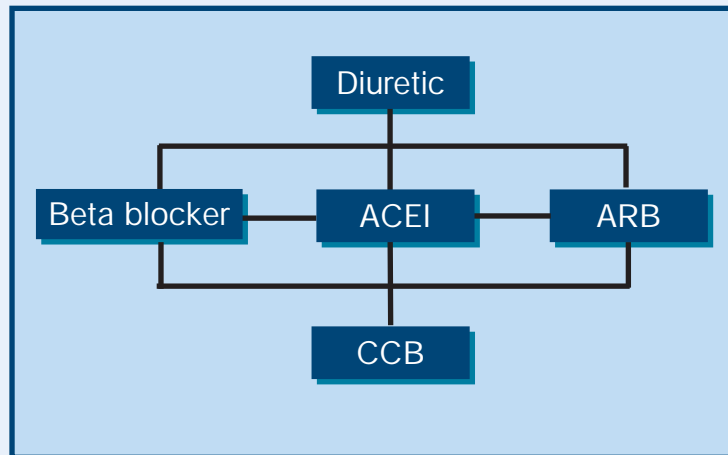


Figure 1a: Use of a diuretic as a first-line drug.

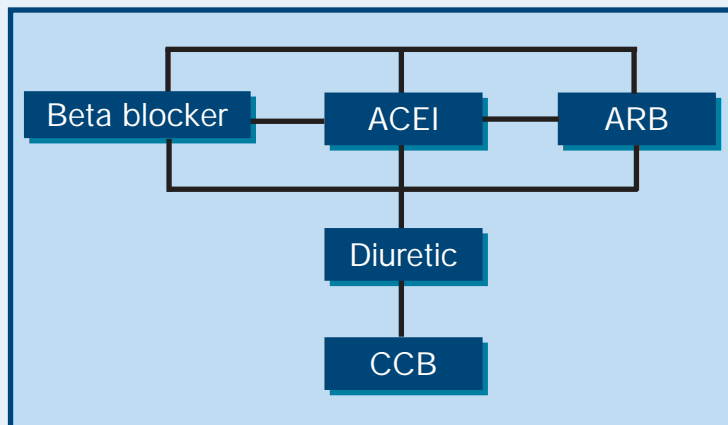


Figure 1b: Use of a beta blocker, ACEI or ARB as a first-line drug.

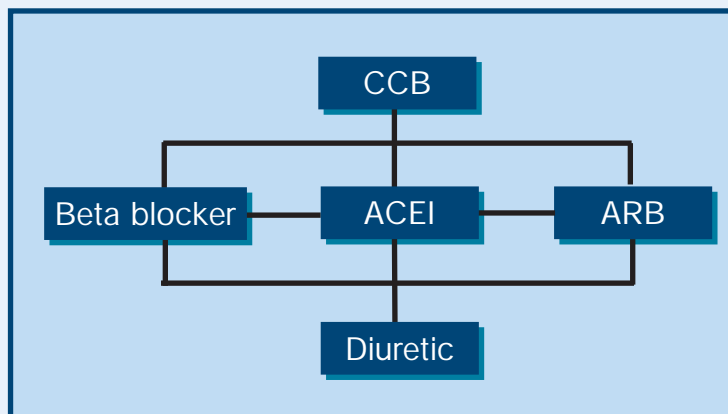


Figure 1c: Use of a calcium channel blocker as a first-line drug.

## ♥ Practical Point

Common causes of a poor response to ACEIs or ARBs include:

- ♥ **High salt intake;**  
(ideal intake < 110 mmol/day);
- ♥ **Too low a dose of diuretic; and**
- ♥ **Giving short-acting loop diuretics only once daily.**

ed them primarily because combination tablets interfered with their ability to titrate the dose of either, or both, medications.

## Why We Should Use Combination Therapy

Most of the newer medications have only one or two dose levels that are commonly used (with the exception of some ACEIs which have higher doses to which we should titrate for patients with CHF and renal disease). Thiazide diuretics are now used at lower doses in order to avoid the electrolyte and metabolic adverse effects commonly seen in the days of “stepped care” therapy. Physicians have accepted that it is better to use the older medications in moderate doses so as to avoid the adverse effects and then add other drugs whose actions complement the first-line medications. Chosen wisely, these combinations enhance BP reduction and increase the probability of reaching target BP. If necessary, a third drug can be added; again, this medication should complement the pharmacologic action of the first two medications, not be redundant.

## Guidelines and Use of Combination Medications

The current hypertension recommendations allow for several different classes of medications to be first-line therapy. The thiazide diuretics are the old standard first-line medication; since their use stimulates the RAAS, the most appropriate second-line medications would be ACEIs or ARBs (which are better disruptors of the RAAS than the older beta blocker medications) (Figure 1a).

ACEIs are the most commonly used medication for hypertension. If the ACEIs are used as first-line therapy (as recommended for patients with renal disease or CHF), then a diuretic would be a good second-line medication. In renal diseases, diuretics have been shown to augment the proteinuria reduction seen when ACEIs and ARBs are used in proteinuric renal diseases (Figure 1b). If ARBs are used as first-line therapy [(as has been recently shown to be useful in diabetic renal disease in such trials as the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and the Irbesartan Diabetic Nephropathy Trial (IDNT) or as losartan has been used in the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study for patients with LVH)], then a diuretic would again be useful as the second-line drug. Poor response to ACEIs or ARBs may be due to a patient eating a diet high in salt and not taking an adequate dose of diuretic. Loop diuretics, like furosemide, should not be used normally in the treatment of hypertension, unless the patient’s renal function is significantly decreased. In that case, loop diuretics should be used twice daily since they are short-acting (at 8 am and 4 pm).

## Combination Therapy in Hypertensive Patients

Table 4

### Drug Combinations for Various Cardio-Renal

Condition	First-line	Second-line	Third-line*
Essential hypertension	Diuretic	ACEI, ARB	CCB, Beta blocker
	ACEI	Diuretic	CCB, Beta blocker
	CCB	ACEI, ARB, Beta blocker	Diuretic
Isolated systolic hypertension	Diuretic or dhp-CCB**	Beta blocker	ACEI or ARB
CHF	ACEI	Diuretic	Beta blocker, dhp-CCB
LVH	ARB	Diuretic	CCB
Renal disease	ACEI	Diuretic	CCB
Diabetic renal disease	ARB	Diuretic	CCB

\* Clonidine is a useful third- or fourth-line drug but adverse effects limit use.  
 \*\* dhp-CCB: dihydropyridine CCB, such as amlodipine or nifedipine.

CCBs have been shown to be as beneficial as diuretic therapy in essential hypertension or isolated systolic hypertension; first-line CCBs might be augmented with the use of beta blockers, ACEIs or ARBs as second-line medications since diuretics have been shown to add little as second-line (Figure 1c).

When hypertension co-exists with other conditions, an initial antihypertensive medication may be recommended as first-line therapy. However, the BP may not reach target with just one medication and another medication may be required. The second medication may be the same as has been previously outlined, but might be specific to the coexistent condition (Table 4).

### Medication Issues that Affect Adherence

Studies on adherence to antihypertensive medications have uncovered several issues

that may be resolved by the use of fixed-dose combination medications.<sup>5</sup> The more tablets patients are prescribed, the more their adherence to medication goes down. If one tablet could contain the same dose of medication as two tablets, the number of tablets would be reduced. Combining medications into one fixed-dose combination tablet would reduce the dispensing fees associated with one medication. This could be a considerable amount if the patient buys prescription medication on a monthly basis or a more modest amount if the medication is purchased on a three-month basis. As it happens, most pharmaceutical companies have not increased the price of the ARB-diuretic fixed-dose combination tablets over the price of the ARB tablet, resulting in greater savings for the patient and/or insurance company. This also results in a greater reduction in BP and risk of cardiovascular event for the same amount of money as single-drug therapy, hence better cost-effectiveness.<sup>6</sup>

### Case Discussion

Since there are no signs of acute heart failure or hemorrhagic changes in the optic fundi, hospitalization is not required.

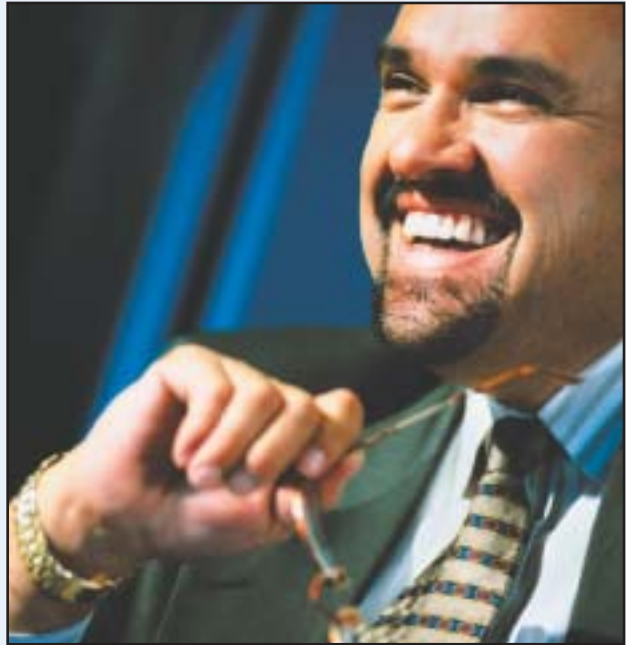
Mr. AE is started on a combination of losartan, 100 mg, and hydrochlorothiazide, 12.5 mg and asked to restart a low-salt diet. He is started on two antihypertensive medications since the reduction from a single medication would have been insufficient. Losartan is chosen because the results of the recent LIFE study demonstrated better results for patients treated with losartan plus a diuretic than for treatment with atenolol plus a diuretic. This is particularly relevant since this patient has been diagnosed previously with LVH.

#### First followup:

Mr. AE was seen three weeks later. At this time, his BP was 158/102, with a pulse of 88 bpm. He had no complaints. Since his blood pressure is not at target ( $< 140/90$ ), verapamil 240 mg, was added to his other medications.

#### Second followup

Mr. AE is seen in four weeks time. His BP is 142/92 with a pulse rate of 82 bpm. It is decided to leave him on the current dose of medication for another four weeks, but the dose of verapamil will be increased at the next visit if the BP is not  $< 140/90$ . He is advised to begin walking every day for a minimum of 30 minutes now, but that the ultimate goal is to walk 50-60 minutes most days of the week, at a speed of 6 km/hour (4 miles/hour). This should help lower BP as well as promote weight loss and an improved sense of energy.



The dose of diuretic used in the fixed-dose ARB-diuretic or ACEI-diuretic combination is low. The adverse effects associated with these combinations are no greater than when the ACEI or ARB is used alone. This means greater BP reduction without side effects.

Patients are more likely to take their medication if they understand why the medication has been prescribed and if they develop a plan on integrating the medication (and/or lifestyle modifications) into their daily life. Therefore, physicians should take a few moments to explain the use of


# Combination Therapy in Hypertensive Patients

the medication(s) and when and how it (they) should be taken.

## Conclusion

The majority of patients with hypertension are going to need more than one medication to lower their BP to target, and hence provide the patient with optimal reduction in the risk of a cardiac or cerebrovascular event. Some combinations of antihypertensive medications make more physiologic sense than others and will provide augmented BP reduction. Some of these combinations are now available as fixed-dose combination tablets.

Although the use of fixed-dose “combos” was frowned upon in the past, it is now advocated for a variety of reasons, many of which are associated with better patient adherence to therapy.

The greatest obstruction to reaching target BP is physician reluctance to either initiate medication or increase medication. To maximize the benefit to the individual patient and to the community we should be more aggressive in combining lifestyle modification and medication, or using combination therapy in the treatment of hypertension.<sup>7</sup> 

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