

This weeks Question:

According to the JNC 7 guidelines, use of fixed low-dose combination therapy with any of several different approved combinations of antihypertensive agents can be recommended. However, for which of the following reasons is fixed-dose therapy not generally applicable?

1. To improve patient adherence to therapy
2. As a "standard of care" for all patients with blood pressure levels > 140/90 mm Hg
3. To minimize side effects by using lowest effective doses of each agent
4. To provide a rapid response in those patients requiring a 20/10-mm Hg decrement in blood pressure levels

Fixed-dose Therapy

One of the important recommendations of the JNC 7 guidelines applies to those patients who are initially diagnosed with blood pressure levels more than 20/10 mm Hg above goal. For these patients, or those whose levels increase to these elevations, the guidelines recommend that consideration should be given to initiating therapy with 2 drugs, either as separate prescriptions "or in fixed-dose combinations."

Thus, one of the important tenets of the new JNC 7 guidelines is that fixed low-dose combinations -- because of their simplicity of use and the fact that they improve the blood pressure response rate while minimizing the incidence of adverse effects -- should be considered as suitable for not only second-line, but even as first-line therapy in those patients requiring a 20/10-mm Hg decrement in blood pressure levels.

Although at present there are no large, well-controlled clinical trial results to distinguish among the various combinations, several fixed-dose combination therapies are currently available for treating hypertension (see Table 2).

Table 2: Fixed-dose Combination Therapies

Combination Type	Fixed-dose Combination (mg)	Trade Name
ACE inhibitors and CCBs	Amlodipine/benazepril HCl (2.5/10, 5/10, 5/20, 20/25) Enalapril maleate/felodipine (5/5) Trandolapril/verapamil (2/180, 1/240, 2/240, 4/240)	<i>Lotrel</i> <i>Lexxel</i> <i>Tarka</i>
ACE inhibitors and diuretics	Benazepril/HCTZ (5/6.25, 10/12.5, 20/12.5, 20/25) Captopril/HCTZ (25/15, 25/25, 50/15, 50/25) Enalapril maleate/HCTZ (5/12.5, 10/25) Lisinopril/HCTZ (10/12.5, 20/12.5, 20/25) Moexipril HCl/HCTZ (7.5/12.5, 15/25) Quinapril HCl/HCTZ (10/12.5, 20/12.5, 20/25)	<i>Lotensin HCT</i> <i>Capozide</i> <i>Vaseretic</i> <i>Prinzide</i> <i>Uniretic</i> <i>Accuretic</i>
ARBs and diuretics	Candesartan cilexetil/HCTZ (16/12.5, 32/12.5) Eprosartan mesylate/HCTZ (600/12.5,	<i>Atacand/HCT</i> <i>Teveten/HCT</i> <i>Avalide</i>

	600/25) Irbesartan/HCTZ (150/12.5, 300/12.5) Losartan potassium/HCTZ (50/12.5, 100/25) Telmisartan/HCTZ (40/12.5, 80/12.5) Valsartan/HCTZ (80/12.5, 160/12.5)	<i>Hyzaar</i> <i>Micardis/HCT</i> <i>Diovan/HCT</i>
Beta blockers and diuretics	Atenolol/chlorthalidone (50/25, 100/25) Bisoprolol fumarate/HCTZ (2.5/6.25, 5/6.25, 10/6.25) Propranolol LA/HCTZ (40/25, 80/25) Metoprolol tartrate/HCTZ (50/25, 100/25) Nadolol/bendroflumethiazide (40/5, 80/5) Timolol maleate/HCTZ (10/25)	<i>Tenoretic</i> <i>Ziac</i> <i>Inderide</i> <i>Lopressor HCT</i> <i>Corzide</i> <i>Timolide</i>
Centrally acting drug and diuretic	Methyldopa/HCTZ (250/15, 250/25, 500/30, 500/50) Reserpine/chlorothiazide (0.125/250, 0.25/500) Reserpine/HCTZ (0.125/25, 0.125/50)	<i>Aldoril</i> <i>Diupres</i> <i>Hydropres</i>
Diuretic and diuretic	Amiloride HCl/HCTZ (5/50) Spironolactone/HCTZ (25/25, 50/50) Triamterene/HCTZ (37.5/25, 50/25, 75/50)	<i>Moduretic</i> <i>Aldactone</i> <i>Dyazide, Maxzide</i>

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HCTZ, hydrochlorothiazide

SOURCE: US Department of Health and Human Services. JNC 7 Express. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

While the recommendation of the JNC 7 is to use a combination that contains a diuretic, and many of the fixed-dose combinations do add either an ACE inhibitor or an ARB to a diuretic, one of the combinations that has been widely marketed, based on formulations created before the current evidence-based guideline announcements, is the combination of a calcium antagonist with an ACE inhibitor. This combination is conceptually attractive^[17] because the calcium antagonist provides primarily arterial vasodilation, whereas the ACE inhibitor adds some venous dilation, a characteristic that applies particularly to the dihydropyridine calcium antagonists, and which produces an almost exclusive arteriolar dilation. Each agent provides theoretical or actual benefits when certain other conditions are present: ACE inhibitors have been shown to have efficacy against left ventricular dysfunction/heart failure, diabetic nephropathy, and postmyocardial infarction, whereas the calcium antagonists provide protection against angina, certain arrhythmias, and various vasospastic conditions. In addition, in theory both agents have beneficial effects on the kidney, heart, and vasculature that are pressure-independent. Further evidence in favor of this combination strategy, albeit without the fixed-dose feature, comes from the recently presented clinical trial, INternational VERapamil SR/trandolapril STudy (INVEST).^[18] In this trial, the ACE inhibitor trandolapril was used as an add-on agent with a nondihydropyridine calcium channel blocker (verapamil) in more than 22,000 hypertensive patients. Per trial design, the results demonstrated equivalence for this combination in reducing CVD mortality in hypertensive patients with coronary disease when compared with a beta-blocker/diuretic combination.

A further example of this combination strategy, in this case as a fixed-dose combination of amlodipine plus benazepril (marketed as *Lotrel*), has been under active investigation in several clinical trials. The first trial, *Lotrel: Gauging Improved Control (LOGIC)*, demonstrated that this

combination alleviated pedal edema (swelling of the feet and legs), a common side effect of amlodipine monotherapy.^[19]

The results of a second trial with this combination, Study of Hypertension and the Efficacy of *Lotrel* in Hypertensive Diabetics (SHIELD),^[20] demonstrated that

- ? Patients with type 2 diabetes taking the combination reached goal blood pressure (<= 130/85 mm Hg) faster than those patients who started with enalapril monotherapy and later had a diuretic added.
- ? The combination provided significantly greater decrements in mean sitting SBP and DBP than monotherapy with enalapril (SBP: -20.5 vs -14.5 mm Hg, $P = .002$; DBP -13.9 vs -9.6 mm Hg, $P = .001$, respectively).
- ? Neither treatment showed any adverse effects on glycemic control.
- ? Both treatment approaches were well tolerated.

Finally, at the 2003 American Heart Association conference, it was announced that a new trial involving nearly 13,000 patients, Avoiding Cardiovascular Events through COMbination Therapy in Patients LIVING with Systolic Hypertension (ACCOMPLISH), would be initiated. The trial will be the first morbidity/mortality trial to initiate therapy with a fixed-dose antihypertensive treatment strategy. Thus, until the anticipated completion date in 2005, a strategy of initiating treatment with a fixed-dose combination of an ACE inhibitor and a calcium antagonist must proceed on the basis of the theoretical considerations outlined above.

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