



# Fixed-dose combination therapy for hypertension: when should this approach be used?

**LAURIE HOWES** MB BS, PhD, FRACP, FCSANZ

**Fixed-dose combination therapy is used for the treatment of hypertension in patients who have not responded adequately to monotherapy.**

MedicineToday 2011; 12(4): 75-77

Several studies have demonstrated that most patients with hypertension will require two or more antihypertensive agents to control their blood pressure.<sup>1,2</sup> Blood pressure targets of less than 140/90 mmHg for patients with uncomplicated hypertension and less than 130/80 mmHg for patients with diabetes or renal dysfunction are now recommended. As a result, fixed-dose combinations of two or even three antihypertensive drugs have become widely used.

## WHAT GPs NEED TO KNOW

### What are the benefits?

Fixed-dose combinations have the advantages of greater patient acceptance, better compliance and lower prescription costs. The use of submaximal doses of two drugs that have different modes of action allows additive effects on blood pressure and vascular protection while minimising or even attenuating the side effects of the individual components.

### Are there disadvantages?

The theoretical disadvantages of fixed-dose therapy are that the titration to optimal doses of each component may not occur or that excessive reductions

in blood pressure may occur. These concerns can be addressed by titration of the individual antihypertensive drugs prior to switching the patient to a fixed-dose combination or, alternately, by titration up to the maximum dose of one of the components before changing to a fixed dose with the lowest dose of the second antihypertensive agent.

### Which ones are available?

The most commonly used fixed-dose combinations are drugs that block the renin-angiotensin system (e.g. ACE inhibitors or angiotensin receptor blockers) with either a low-dose diuretic (e.g. hydrochlorothiazide, indapamide) or a calcium channel blocker (e.g. amlodipine, lercanidipine, verapamil). A list of fixed-dose combinations for hypertension is presented in the Table.

### Are there any preferred combinations?

Recent studies have suggested that combinations of ACE inhibitors or angiotensin receptor antagonists with amlodipine may provide better blood pressure control and superior outcomes than combinations of ACE inhibitors or angiotensin receptor antagonists with diuretics.<sup>3,4</sup>

Professor Howes is a Pre-eminent Consultant Physician, Gold Coast Hospital and Professor of Pharmacology and Therapeutics, Griffith and Bond University Medical Schools, Gold Coast, Qld.

**TABLE. FIXED-DOSE COMBINATIONS OF ANTIHYPERTENSIVE DRUGS AVAILABLE**

Combination	Trade name
<b>ACE inhibitor combinations</b>	
Enalapril, hydrochlorothiazide	Enalapril/HCT Sandoz, Renitec Plus
Enalapril, lercanidipine	Zan-Extra
Fosinopril, hydrochlorothiazide	APO-Fosinopril HCTZ, Fosetic, Fosinopril/HCT Sandoz, Fosinopril/HCTZ-GA, Hyforil, Monoplus
Perindopril, indapamide	Chemart Perindopril/Indapamide, Coversyl Plus, Generex Perindopril/Indapamide, Perindo Combi, Terry White Chemists Perindopril/Indapamide
Perindopril, amlodipine	Coveram, Reaptan
Quinapril, hydrochlorothiazide	Accuretic
Ramipril, felodipine	Triasyn
Trandolapril, verapamil	Tarka
<b>ARB combinations</b>	
Candesartan, hydrochlorothiazide	Atacand Plus
Eprosartan, hydrochlorothiazide	Teveten Plus
Irbesartan, hydrochlorothiazide	Avapro HCT, Karvezide
Olmesartan, hydrochlorothiazide	Olmotec Plus
Olmesartan, amlodipine	Sevikar
Telmisartan, hydrochlorothiazide	Micardis Plus
Valsartan, amlodipine	Exforge
Valsartan, hydrochlorothiazide, amlodipine	Exforge HCT
Valsartan, hydrochlorothiazide	Co-Diovan

ABBREVIATIONS: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

**How are they used?**

Combination therapy should not be used to initiate therapy. They may be used in patients already controlled on the combination as individual tablets. Alternately, patients may be titrated up to the maximum recommended dose of one drug prior to switching to a combination of the equivalent dose of that drug plus the lowest dose available of the second drug. If blood pressure remains uncontrolled, titration up to higher strengths of the second drug should occur.

If blood pressure still remains uncontrolled, switching to the triple therapy

combination of valsartan, amlodipine and hydrochlorothiazide is an option. Alternately, a third drug that is not being used in the fixed-dose dual combination can be added.

**What is the efficacy?**

Combination therapies are chosen to have additive effects on blood pressure. For example, the combination of the angiotensin receptor antagonist olmesartan and amlodipine has additive effects across the range of combinations available (Figure).<sup>5,6</sup>

The use of combination therapies may

also attenuate the side effects that occur with monotherapy. The adverse metabolic effects of hypokalaemia and impaired glucose tolerance that occur with hydrochlorothiazide are abolished by combination with an ACE inhibitor or angiotensin receptor antagonist.<sup>7</sup> The ankle oedema that is associated with amlodipine therapy is attenuated by combination of this drug with an ACE inhibitor or angiotensin receptor antagonist.<sup>5,6</sup>

**What needs monitoring?**

Blood pressure should be carefully monitored in patients with hypertension after the initiation of combination therapy because significant hypotension and dizziness may occur. Renal function should be assessed within the first week of therapy in patients who have not received angiotensin receptor antagonist or ACE inhibitors previously because the use of these drugs may produce acute renal failure in patients with bilateral or unilateral renal artery stenosis. Serum potassium levels should also be monitored as levels may increase in patients taking an ACE inhibitor or angiotensin receptor therapy, particularly in those with diabetes or renal impairment and in those receiving concomitant NSAID drug therapy.

**Common side effects**

Combination therapies are generally very well tolerated. The most frequently encountered side effect is ankle oedema with formulations containing amlodipine. However, this occurs less frequently in patients taking combination therapy than in those taking amlodipine monotherapy.<sup>5,6</sup> Combination therapy with ACE inhibitors may cause cough. Combinations of angiotensin receptor antagonist with hydrochlorothiazide have tolerability similar to placebo but these combinations may not be as effective in reducing vascular events as combinations with amlodipine.<sup>4</sup> Dizziness may also occur but this is generally due to excessive blood pressure reduction.

## Precautions

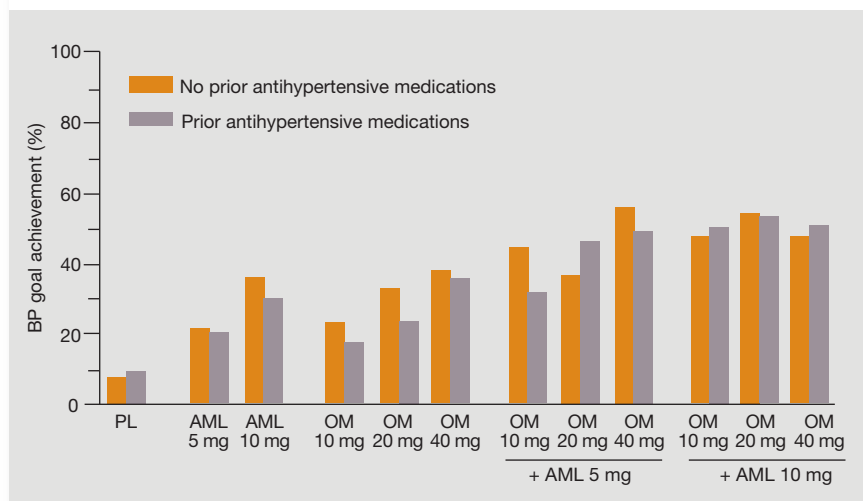
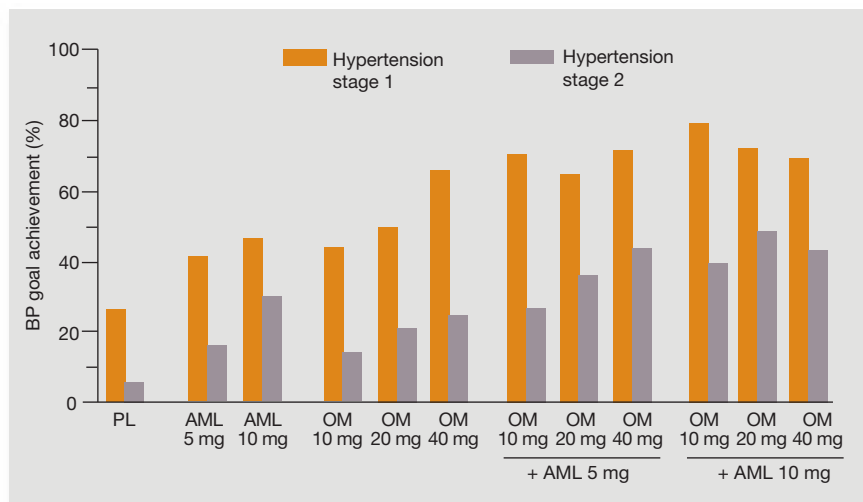
Significant interactions may occur with drugs that inhibit cytochrome P450 (CYP 3A4) and with grapefruit juice when amlodipine is used in the combination. This is because amlodipine is in part metabolised by CYP 3A4 and elevated levels of amlodipine may occur, causing an increase in blood pressure reduction.

## SUMMARY

In summary, fixed-dose combination therapy of hypertension is a useful option for patients who have uncontrolled hypertension while taking monotherapy. **MI**

## REFERENCES

- Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood pressure lowering and low dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; 351: 1755-1762.
- ALLHAT Officers and Co-ordinators for the ALLHAT Collaborative Research Group. The antihypertensive and lipid lowering treatment to prevent heart attack trial. Major outcomes in high risk hypertensive patients randomised to angiotensin converting enzyme inhibitor or calcium channel blocker versus diuretic: the Anti-hypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial. *JAMA* 2002; 288: 2981-2997.
- Dahlof B, Sever PS, Poulter NR, et al; ASCOT investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA): a multi-centred randomised controlled trial. *Lancet* 2005; 366: 895-906.
- Weder AB. Avoiding cardiovascular events through combination therapy in patients living with systolic hypertension: a comparison of first line combination therapies. *Exp Opin Pharmacother* 2005; 6: 275-281.
- Chrysant SG, Melino SG, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling blood pressure: COACH, a randomised double blind, placebo controlled 8-week factorial efficacy and safety study. *Clin Ther* 2008; 30: 587-604.



**Figure. Additive effects of amlodipine and olmesartan in patients with hypertension demonstrated as the percentage of patients achieving blood pressure goal. a (top). Patients with stage 1 hypertension and patients with stage 2 hypertension. b (bottom). Patients taking prior antihypertensive therapy and patients not receiving prior antihypertensive therapy.<sup>6</sup>**

ABBREVIATIONS: AML = amlodipine; BP = blood pressure; OM = olmesartan; PL = placebo.

- Oparil S, Lee J, Karki S, et al. Subgroup analysis of an efficacy and safety study of concomitant administration of amlodipine besylate and olmesartan medoxomil: evaluation by baseline hypertension stage and prior antihypertensive medication use. *J Cardiovasc Pharmacol* 2009; 54: 427-436.
- Plat F, Saini R. Management of hypertension: the role of combination therapy. *Am J Hypertens* 1997; 10: 262S-271S.

This article is for general information purposes only, and the full product information should be consulted before prescribing any of the mentioned medications.

COMPETING INTERESTS: Professor Howes has received honoraria and clinical trial funding from a number of pharmaceutical companies. These have not influenced the preparation of this article.