

# Choosing antihypertensive treatment for a South African population

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## Abstract

There is no uniform agreement as to which antihypertensive drugs should be given for initial therapy. All of the antihypertensive agents are roughly equally effective, producing a good antihypertensive response in 30 to 50 percent of cases. Thus, in uncomplicated cases, the choice of an antihypertensive drug is not generally made on the basis of efficacy. There is, however, wide inter-patient variability as many patients will respond well to one drug but not to another. There are also some predictable differences, such as black patients generally responding better to monotherapy with a thiazide diuretic or calcium channel blockers (CCBs), and relatively poorly to ACE (angiotensin-converting enzyme) inhibitors or beta blockers.

**SA Fam Pract 2007;49(8): 27-30**

### Introduction

The choice of agent(s) is determined by the ability to achieve the ultimate goal of antihypertensive therapy: to maximally reduce cardiovascular risk without compromising quality of life.

Although the different drugs have relatively unique qualities, no antihypertensive agent is perfect. Nevertheless, currently available choices are highly effective, and when used properly, can protect almost all patients without inducing significant adverse effects. There is a potential problem in both the government and private sectors in that there are many restrictive formularies that frequently provide only for the least expensive drugs, even if they are not the most appropriate for an individual's needs.

As more patients with mild hypertension are being treated with drugs, the choice of therapy, particularly of the initial drug, should be made with care. The first drug chosen may have to be taken for decades. Therefore, adverse effects that may not be obvious must be considered. However, as noted in virtually all trials, most patients will need more than one drug to control their hypertension.

### Initial therapy

The SAHS (South African Hypertension Society) and National Department of Health Hypertension Guideline<sup>1</sup> recommendation for initiating therapy in uncomplicated hypertension is with a low-dose thiazide diuretic unless there is a specific indication for a drug from another class. It is reasonable to conclude

that thiazide diuretics provide similar cardiovascular benefits in this setting.

This recommendation applies to low doses of a thiazide diuretic (e.g. 12.5 to 25 mg of hydrochlorothiazide). This regimen is associated with a low rate of metabolic complications, such as hypokalaemia, glucose intolerance, and hyperuricaemia. However, severe hyponatraemia has been observed.

Thiazides have other actions that may be desirable in specific patient populations. In particular they lower urinary calcium excretion, which may be beneficial in patients with hypercalciuria and recurrent calcium stones, and in those with osteoporosis.

If low-dose thiazide monotherapy fails to attain goal blood pressure in uncomplicated hypertensives, an ACE inhibitor or ARB (angiotensin receptor blocker) or calcium channel blocker can be added sequentially.

The suggestion that calcium channel blockers may increase the risk of myocardial infarction in hypertensive patients has not been confirmed in studies using long-acting dihydropyridine. The appropriate use of these drugs should therefore not be curtailed.

### Monotherapy based upon age and race

The likelihood of a good response is increased when two simple clinical characteristics, age and race, are utilised to determine drug treatment. The following patients respond best to different types of antihypertensive agents used as

monotherapy:

- Younger white patients to beta blockers and ACE inhibitors (and probably ARBs)
- Older and black patients to diuretics and CCBs

Support for this differential antihypertensive response with age is supported by a study of 56 young white hypertensive patients that evaluated the efficacy of a cross-over rotation among four main classes of drugs. Significantly greater responses in both systolic and diastolic blood pressure levels were noted with the ACE inhibitor and beta blocker than with the CCB or diuretic.

The greater efficacy of the CCBs and diuretics in elderly white and black hypertensives has also been documented. The response of these patients to an ACE inhibitor or a beta blocker can be enhanced by the addition of a diuretic. These different responses may be at least partially related to the baseline plasma renin activity (PRA) level.

The ASCOT<sup>2</sup> study, however, suggests that beta blockers (atenolol) should not be used as first line therapy for the treatment of hypertension in the absence of other indications for their use.

### Response rates to single drug therapy for hypertension in blacks over the age of 60 years. (Figure 1)

The highest response was noted with diltiazem and hydrochlorothiazide (HCTZ) and the lowest with captopril. A response was defined as a diastolic pressure be-

Figure 1: Single drug in blacks

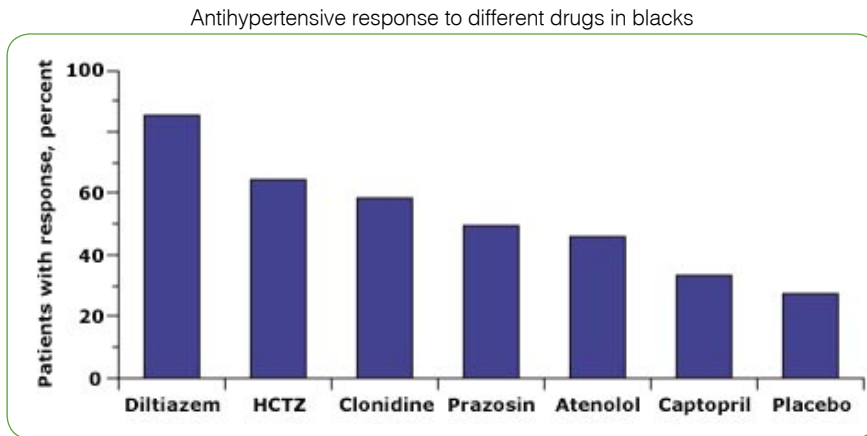
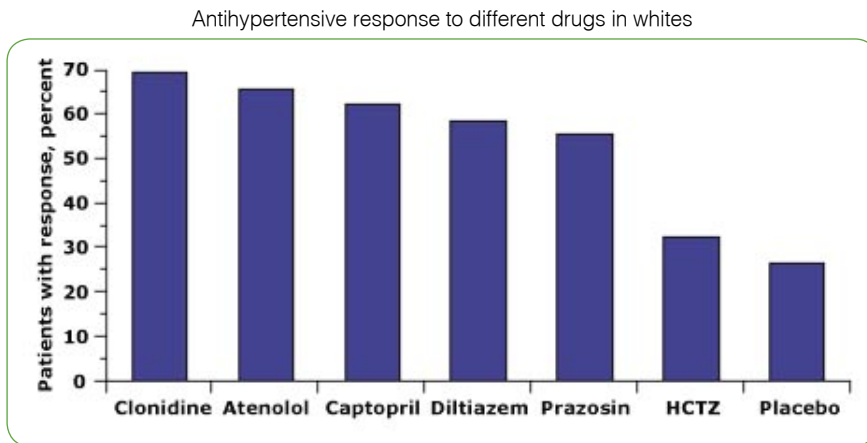


Figure 2: Single drug in whites



low 90 mmHg at the end of the titration phase and below 95 mmHg at one year. The pattern of response was similar but the success rate for each drug was reduced by five to fifteen percent if goal diastolic pressure was less than 90 mmHg at one year. There were between 42 and 53 patients in each group.<sup>3</sup>

**Response rates to single drug therapy for hypertension in whites under the age of 60. (Figure 2)**

There were no significant differences in response, except that hydrochlorothiazide (HCTZ) appeared to be least effective. A response was defined as a diastolic pressure below 90 mmHg at the end of the titration phase and below 95 mmHg at one year. The pattern of response was similar but the success rate for each drug was reduced by five to fifteen percent if goal diastolic pressure was less than 90 mmHg at one year. There were between 30 and 39 patients in each group.<sup>3</sup>

**Refining drug choices**

Any drug that lowers blood pressure unless absolutely contraindicated will con-

fer protection against target-organ damage. However, the following classes of drugs have additional protective properties in the case of the listed associated clinical conditions/target-organ damage.

These general recommendations for initial therapy should be amended in certain clinical settings in which specific agents might offer particular benefits (See Table 1). These indications include the demonstration that ACE inhibitors improve outcomes in a number of high risk settings and that beta blockers improve survival in patients with systolic heart failure (third-generation beta blockers) and a prior myocardial infarction.

**ACE inhibitors**

ACE inhibitors are first-line therapy in all patients who have heart failure or asymptomatic left ventricular dysfunction, in all patients who have had an S-T elevation myocardial infarction (STEMI), in patients with a non S-T elevation myocardial infarction (non-STEMI) who have had an anterior infarct, diabetes, or systolic dysfunction, and in patients with proteinuric chronic renal failure. Combination therapy with an ARB appears to be beneficial in patients with heart failure and proteinuric chronic renal failure.

It has been suggested that ACE inhibitors and ARBs have a cardioprotective effect independent of blood pressure lowering in patients at high risk for a cardiovascular event.

**Indications for specific drugs**

Table I: Recommendations on compelling indications for a specific drug class<sup>1</sup>

Compelling indications	Drug class
Angina	Beta blocker OR CCB (rate lowering preferred)
Prior myocardial infarct	Beta blocker AND ACE-I (ARB if ACE-I intolerant). Verapamil if beta blockers contraindicated. If heart failure, see below
Heart failure	ACE-I (ARB if ACE-I intolerant) AND certain beta blockers AND aldosterone antagonist For combination ARB and ACE-I * Loop diuretics for volume overload
Left ventricular hypertrophy (confirmed by ECG)	ARB (preferred) OR ACE-I
Stroke: secondary prevention	Low-dose thiazide-like diuretic and ACE-I or ARB
Diabetics type 1 or 2 with or without evidence of microalbuminuria or proteinuria	ACE-I OR ARB – usually in combination with a diuretic
Chronic kidney disease	ACE-I or ARB – usually in combination with a diuretic
Isolated systolic hypertension	Low-dose thiazide or thiazide-like diuretics OR long-acting CCB

<sup>1</sup> Young JB, Dunlap ME, Pfeffer MA, et al. Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Investigators and Committees. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. *Circulation* 2004; 110:2618-2626.

### ARBs

The indications for, and efficacy of ARBs and ACE inhibitors are much the same. An ARB is particularly indicated in patients who do not tolerate ACE inhibitors (mostly because of coughing).

There is at least one setting in which ARBs have specific benefits and in which similar trials have not been performed with ACE inhibitors: severe hypertension with ECG evidence of left ventricular hypertrophy in LIFE.<sup>4</sup> An ARB can be used instead of an ACE inhibitor in such patients, although it is probable that an ACE inhibitor would be equally effective.

### Beta blockers

A beta blocker without intrinsic sympathomimetic activity should be given after an acute myocardial infarction and to stable patients with heart failure or asymptomatic left ventricular dysfunction (beginning with very low doses to minimise the risk and degree of initial worsening of myocardial function). The use of beta blockers in these settings is in addition to the recommendations for ACE inhibitors in these disorders.

Beta blockers are also given for rate control in patients with atrial fibrillation, for control of angina, and for symptom control in a number of other disorders.

Compared to other antihypertensive drugs, during the primary treatment of hypertension, beta blockers may be associated with a small absolute increase in the stroke rate (particularly among smokers) and perhaps, with atenolol, a small increase in mortality. Thus, in the absence of a specific indication for their use, beta blockers should not be used as primary therapy for hypertension.

### Diuretics

A thiazide diuretic should be prescribed in the absence of an indication for any other specific drug(s) or when goal blood pressure has not been attained.

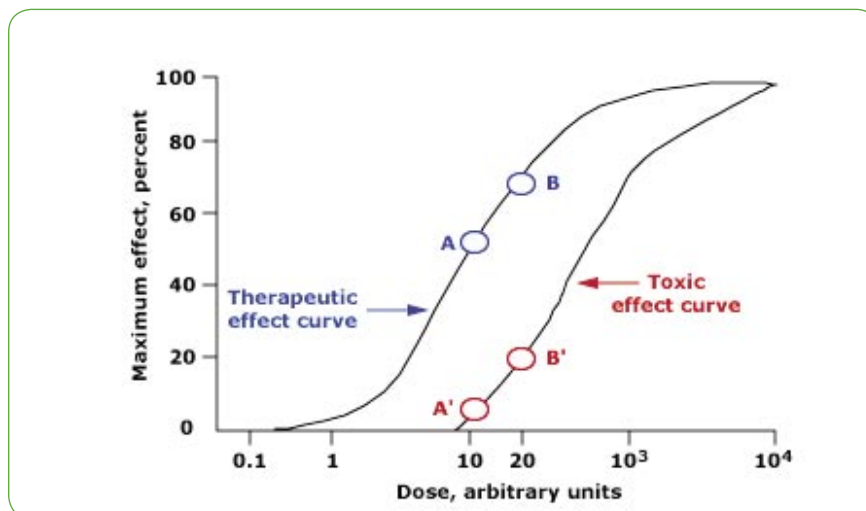
Diuretics should also be given for fluid control in patients with heart failure or nephrotic syndrome; these settings usually require loop diuretics. In addition, an aldosterone antagonist is indicated in patients with advanced heart failure who have relatively preserved renal function and, in patients with less severe disease, for the treatment of hypokalaemia.

### Calcium channel blockers

There are no absolute indications for calcium channel blockers in hyperten-

**Figure 3:** Dose response curves in hypertension.

Dose relation between therapeutic effect and toxicity with antihypertensive drugs



sive patients. Like beta blockers, they can be given for rate control in patients with atrial fibrillation or for control of angina.

### Other specific settings

Beyond these indications, a number of specific recommendations can be made for drugs with favourable effects in various settings. As an example, an alpha blocker may be preferred in older men with symptoms of prostatism.

### Drug dosing and drug frequency

The steepest part of the dose response curve is frequently seen at lower doses: Good responders generally respond to low doses with few side effects, while higher doses produce more side effects often with little further reduction in blood pressure.

The theoretical therapeutic and toxic effect curves of antihypertensive agents vary based upon the administered dose. The theoretical effects of a single drug given at two different doses (10 and 20 units) are shown in figure 3. At a dose of 10 units, the antihypertensive agent has a minimal toxic effect (A') and a moderate therapeutic effect (A). Doubling the dose, however, is associated with substantial toxic effects (B') but little increase in therapeutic efficacy (B).<sup>5</sup>

The issue of dose frequency relates to the absence of 24 hour efficacy with certain "long-acting" drugs such as the angiotensin-converting enzyme inhibitor enalapril. Once daily dosing gives a greater peak response, but the blood pressure tends to return toward baseline in the early morning hours prior to

the next dose. This is of concern, since a greater daily blood pressure load and early morning abrupt elevation in blood pressure can increase cardiovascular risk.

Giving half the dose twice a day produces a lesser peak effect but a more sustained response; however, adherence may be reduced. Drugs that are longer-acting, either by inherent properties or special delivery systems, are the better choice. It is prudent, however, to check the blood pressure in the morning prior to the next dose whenever a once daily regimen is used.

### Combination therapy

Administering two drugs as initial therapy should be considered in patients with blood pressure that is more than 20/10 mmHg above goal blood pressure. This strategy may increase the likelihood that target blood pressure is achieved in a reasonable time period, but should be used cautiously in patients at increased risk for orthostatic hypotension (such as diabetics and the elderly).

In patients with mild hypertension, the first-line agent will normalise the blood pressure in up to 50 percent of patients. A second drug should be considered if there is a suboptimal response to initial therapy. The rationale behind a combination regimen is that early addition of a second drug may be: (1) as or more effective, since many responders to a given drug do so at relatively low doses; and (2) associated with less toxicity.

Most drug combinations, using agents that act by different mechanisms, tend to have an additive effect. Examples include an ACE inhibitor with

a diuretic or calcium channel blocker. A low dose of a thiazide diuretic increases the antihypertensive effect of all other antihypertensive drugs by minimising volume expansion.

An ACE inhibitor or ARB also minimises diuretic-induced metabolic abnormalities (such as hypokalaemia, hyperuricaemia and hyperlipidaemia) and prevents the hypovolaemia-induced increase in angiotensin II that normally limits the response to the diuretic.

**Potentially unfavourable combinations**

Some drug combinations may not have an additive antihypertensive effect, such as the combination of an ACE inhibitor and a beta blocker, or a diuretic and a calcium channel blocker. The relative lack of efficacy may be explained in part by similar mechanisms of action which could contribute to a lesser additive value when used as combinations.

There are also combinations that have deleterious side effects. In particular, a beta blocker should be used with caution in combination with nondihydropyridine CCBs. These drugs can lead to profound bradycardia or heart block. A beta blocker diuretic combination is diabetogenic and should be avoided especially in obese individuals and those with a family history of diabetes mellitus.



In general, however, therapy should start with a single drug unless the blood pressure is more than 20/10 mmHg over the goal. 🙋

See CPD Questionnaire, page 42

**P** This article has been peer reviewed

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