

Keywords:
hypertension,
treatment
targets,
drug
combinations,
third-line agents

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Accepted for
publication
18th June 2002

JRAAS 2002;3:103-8

**Journal of
the Renin-
Angiotensin-
Aldosterone
System**
(Including other
peptidergic systems)

June 2002
Volume 3
Number 2

The frequent need for three or more drugs to treat essential hypertension. What evidence for optimal combinations?

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Abstract

Treatment of high blood pressure (BP) reduces the risk of death and morbidity from stroke and coronary heart disease. There is accumulating evidence from large outcome studies that support a move towards lower treatment targets in hypertensives, particularly for those with concomitant risk factors or evidence of established target organ damage. At present, the achieved rates for BP control in the UK are very poor. Amongst the many possible reasons for poor BP control is the under utilisation of effective drug combinations. This article addresses the rationale for two and three drug combination therapy in hypertension and reviews the trial evidence for efficacy of combinations.

Introduction

High blood pressure (BP) is associated with an excess risk of premature death. In patients with hypertension, BP reduction will reduce mortality from stroke and coronary heart disease.¹ With successive outcome trials in hypertension and cardiovascular disease, it has become clear that the lower the BP achieved with treatment, the greater the cardiovascular protection afforded.^{2,3} Thus, the trend for treatment targets, in those who have been identified as requiring BP-lowering therapy, is for them to become ever lower, particularly in diabetics and individuals with pre-existing cardiac or renal disease, who are at even higher risk.

At the present time, there is no unified international consensus on treatment targets, either for uncomplicated hypertensives or for subgroups with relatively higher cardiovascular risk profiles. Table 1 summarises the current treatment targets issued by the major expert panels.^{4,6} The commitment to meet these targets, in a greater proportion of our patients, will be a major financial and clinical undertaking for governments and healthcare providers respectively.

Hypertension is firmly established as an independent risk factor for cardiovascular disease. It is, however, the fact that hypertension is so common that accounts for it being one of the leading causes of premature death and disability in the developed world.⁷ Estimates from a health survey in England for 1998 suggest a 37% prevalence of hypertension, according to the updated 1999 BHS definitions, (systolic blood pressure [SBP] ≥ 140 mmHg, or diastolic blood pressure [DBP] ≥ 90 mmHg).⁸ Among those with hypertension, treat-

ment and control rates (BP $\leq 140/85$ mmHg) were 32% and 9%, respectively. Where individuals were on drug treatment, 60%, 33% and 7% received one, two and three or more drugs, respectively. Thus, less than one-third of hypertensives received any drug treatment, and the majority of those treated only received monotherapy. In the UK, therefore, there is a substantial proportion of hypertensives with an excess cardiovascular risk attributable to poorly controlled BP. The estimated rates of BP control from the English survey compare relatively poorly with those of other industrialised nations.⁹

The reasons for failure to achieve better rates of BP control are likely to be complex and may involve shortcomings by doctors, patients and the drugs themselves. Large intervention trials, including Hypertension Optimal Treatment (HOT),¹⁰ Swedish Trial in Old Patients with Hypertension-2 (STOP-2),¹¹ Systolic Hypertension in Europe (Syst-Eur),¹² and more recently the Losartan Intervention For Endpoint reduction in hypertension study (LIFE),¹³ make it clear that if BP targets are to be reached, then the majority of patients will need to take two or more antihypertensive agents in combination. The frequent need for drug combinations is probably best illustrated by the HOT study, in which over 75% of participants required dual therapy. In addition, more than 20% required triple therapy with a calcium channel blocker (CCB), plus either an angiotensin-converting enzyme (ACE) inhibitor or β -blocker plus diuretic, in order to achieve a DBP target ≤ 85 mmHg.¹⁰ In the LIFE study, the vast majority (90%) required two drugs to meet a BP target of $<140/90$ mmHg, while over 20% were on three or more antihypertensives.¹³ Furthermore, in a review of clinical trials that randomised patients with either diabetes or renal insufficiency to two different BP targets, Bakris calculated that the group who were randomised to lower target levels of BP required an average of 3.2 antihypertensive drugs.¹⁴

Unfortunately, there is little evidence from well-designed clinical trials to help guide the choice of agents to use in combination, either in terms of BP-lowering capacities of combinations or, more importantly, in terms of clinical outcome.

Which agents to achieve target BP? What the guidelines say

The question as to which agents should be used as

Table 1 Blood pressure targets for treatment in hypertension (mmHg).

Agency	Uncomplicated hypertension	Diabetes	Renal disease	Proteinuria*
BHS	<140/85	<140/80	<130/85	<125/75
JNC VI	<140/90	<130/85	<130/85	<125/75
WHO-ISH	<130/85 young & middle age <140/90 elderly	<130/85	<130/80	<125/75

BHS = British Hypertension Society;⁴ JNC VI = Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, the sixth report;⁵ WHO-ISH = World Health Organisation-International Society of Hypertension.⁶ * Urinary protein excretion >1g/24 hours.

first-line therapy in uncomplicated hypertensives and in more complex hypertensive populations, such as diabetics or individuals with previous coronary events, LVH or renal disease, is an important issue. There is constant debate as to which agents may or may not confer additional clinical and survival advantages beyond, or in addition to, BP-lowering. Interestingly, the three sets of published guidelines⁴⁻⁶ make some attempt to suggest different agents for first-line antihypertensive therapy. The recommendations take into account the presence of target organ damage and co-morbidity, together with the corresponding evidence for reduction of cardiovascular risk with the individual agents. The evidence for specific indications, contra-indications and cautions that apply to different classes of antihypertensive agents is beyond the scope of this article. However, where there is no compelling indication for a specific agent, there may still be reasons for choosing one drug class over another, and these may include socio-economic factors in different countries and likely variations in individual responses to different agents. A rotational study has demonstrated considerable variability in hypertensive patients' response to four classes of antihypertensive agents, including ACE inhibitors (ACE-I) (A), β -blockers (B), CCBs (C) and diuretics (D).¹⁵ There was a significant correlation in the magnitude of responses observed between treatment with the ACE-I and β -blocker, which both block the renin-angiotensin system (RAS), and between treatment with the CCB and diuretic, which act as vasodilator and natriuretic, respectively. In this study, the BP response to ACE inhibition correlated with plasma renin activity (PRA). In a larger study of 1292 hypertensive males, it was found that a CCB was the most effective of six drug classes in blacks. In younger and older whites, an ACE-I and β -blocker were respectively the most effective antihypertensive drugs.¹⁶ All six drugs, however, were superior to placebo in all patient groups, indicating that each has a valuable therapeutic effect, which is independent of age or ethnicity. In general, patients with a higher PRA, i.e. young white individuals, tend to respond well to ACE-I and β -blockers, whereas those with an inactive RAS, i.e. the elderly and black individuals, respond better to either CCBs or diuretics. Where there is a hard indication for a particular drug class,

however, it should not be withheld on the grounds of a relatively poor predicted BP response.

None of the guidelines give clear recommendations on which drugs to use in combination when BP is poorly controlled on monotherapy. In hypertensives, it is still true that the single most important strategy is to lower BP and thereby lower the cardiovascular risk. Absolute BP is more important than the agent used to achieve control. Current guidelines have placed too much emphasis on first-line therapy and have failed to stress that most individuals will require combination therapy to reach treatment targets.

When BP is difficult to control, the JNC VI guidelines suggest that three agents from different classes should be used, one of which should be a diuretic, before hypertension is classified as resistant.⁵ The WHO-ISH guidelines make no recommendations beyond using combination therapy in adequate doses.⁶ The BHS guidelines are more explicit in suggesting that 'rational drug combinations' are used for dual therapy.⁴ The BHS go on to say that commonly used combinations are diuretic, ACE-I and CCB or diuretic, β -blocker and CCB.

Rational two drug combinations and the evidence

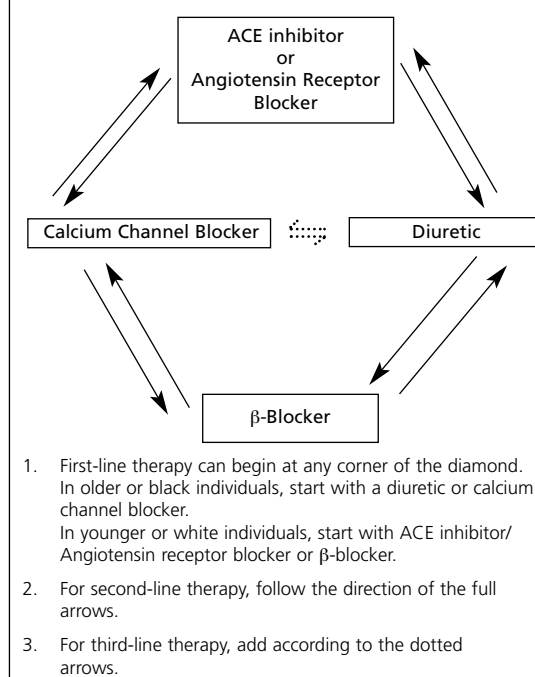
Hypertension is multifactorial in aetiology and individuals are heterogeneous in their response to different treatment strategies. The antihypertensive effect of a single agent is limited by physiological feedback mechanisms, which oppose the action of the drug. In this respect, the most effective way to control BP is to combine agents which lower BP by different mechanisms. Rational combinations for drugs in hypertension will have additive effects on BP-lowering and organ protection and will have minimal or no side-effects. Antihypertensive agents fall into different groups according to their respective mechanism of action. Any two drugs can be combined to lower BP, even if they have similar mechanisms of action, such as an ACE-I and angiotensin receptor blockers (ARB),¹⁷ but the additive effect will be less than the sum of the effect of the two single agents. In general, agents that inhibit the RAS, such as ACE-I, ARBs and β -blockers, combine well with natriuretics and/or vasodilators. This gives rise to four rational combinations for dual therapy, which are summarised in Table 2.

Table 2 Rational two drug combinations for treatment of high blood pressure.

ACE inhibitor/ Angiotensin receptor blocker	+	Diuretic
ACE inhibitor/ Angiotensin receptor blocker	+	Calcium channel blocker
β -blocker	+	Diuretic
β -blocker	+	Calcium channel blocker

In terms of BP-lowering efficacy, all of the above combinations are probably equally efficacious but the first-line agent will be determined according to individual co-morbidity such as diabetes, renal disease, ischaemic heart disease (IHD) or left ventricular hypertrophy (LVH). A randomised, double-blind study has previously compared the BP-lowering efficacy of various fixed-dose drug combinations.¹⁸ The reduction in BP was equivalent when a low-dose combination of ACE-I plus CCB (trandolapril/verapamil SR) was compared with two other recognised fixed-dose combinations, including atenolol/chlorthalidone and lisinopril/hydrochlorothiazide. All three combinations were more effective than placebo and were well tolerated. The majority of studies have demonstrated that the addition of CCBs to diuretics has little additional BP-lowering effect.^{19,20} Similarly, combinations of β -blocker and ACE-I have failed to show consistent additive effects on BP reduction,^{21,22} unless perhaps in the presence of a relatively high resting heart rate.²³

In terms of mortality endpoints from outcome studies, there has been little to support one drug regimen over another, until the publication of the LIFE study.¹³ This trial compared the ARB, losartan, with atenolol in hypertensives with LVH. Less than 10% of participants were controlled on the drug to which they had been randomised, as most required the addition of at least one other agent to achieve the treatment target. The second-line agent in both groups was hydrochlorothiazide, so the majority will have received either a β -blocker/thiazide or an ARB/thiazide combination. Results favoured the ARB-based regimen in terms of a 14.6% reduction in relative risk ($p=0.009$) of the composite primary endpoint, which included cardiovascular mortality, fatal and non-fatal myocardial infarction (MI) and stroke. The majority of this treatment effect was attributable to a reduction in relative risk of fatal and non-fatal stroke in the ARB-treated group. Given the proportion of participants on dual therapy, it would be reasonable to conclude that the ARB/thiazide is a better combination than β -blocker/thiazide in hypertensives with LVH. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is a large prospective study, comparing a CCB/ACE-I regimen with the older β -blocker/diuretic regimen in the primary prevention of coronary heart disease in hypertensive patients.²⁴ It is due to complete in the next 2-3 years and will provide

Figure 1 The modified 'St. George's Diamond' for addition of a third-line antihypertensive drug.

further important information on the relative efficacies of these particular drug combinations.

Rational three drug combinations and the evidence

There is less literature on the use of three drug combinations in hypertension. A commonly held view is that an ACE-I plus diuretic and CCB is the most rational, and indeed preferred, three-drug combination. The other rational combination includes a β -blocker, diuretic and CCB. The St. George's 'Imploding Diamond', was first proposed in 1999 as an aid to prescribing third-line drug therapy in hypertension and is shown here in a modified format (Figure 1).²⁵

Individuals with high BP, requiring three or more drugs, might well be expected to have a relatively high risk of cardiovascular events. There is evidence, however, that the individual outcome depends more on the BP achieved than on the pre-treatment BP.²⁶ Therefore, smaller studies looking at the relative BP-lowering capacities of defined drug combinations, as a surrogate endpoint, might be a reasonable substitute for large outcome studies in this population. There are, in fact, quite a number of studies looking at the BP-lowering effects of multiple drug combinations in hypertension, but the majority of these are small and poorly controlled and most are now outdated.

In the 1980s, the Glasgow Blood Pressure Clinic group published the results of a randomised open study, which compared hydralazine, labetalol, methyl dopa, minoxidil, prazosin and placebo as third-line antihypertensives, when BP was uncontrolled ($>140/95$ mmHg) on a β -blocker/diuretic combination.²⁷ They found that all five

drugs lowered BP significantly more than placebo, with no difference between hydralazine, labetalol, methyldopa and prazosin. Minoxidil achieved a significantly greater reduction in BP than the other agents but caused problematic fluid retention, particularly in individuals with more severe hypertension. Hydralazine was the best-tolerated third-line drug in this study. Following on from this study was a randomised, double-blind, parallel group multicentre study in 120 patients with moderate-to-severe hypertension. The combination of an ACE-I, thiazide diuretic plus methyldopa, (given as first-, second- and third-line respectively) was compared with 'standard triple therapy' with a thiazide, β -blocker and hydralazine.²⁸ The two regimens caused similar reductions in SBP and DBP, but the ACE-I based regimen was better tolerated.

As new drugs became available for the treatment of hypertension, inevitably they too were 'added on' as third-line agents to the β -blocker/diuretic regimen as an escalation of the step-care approach to BP management. As such, the newer drugs were compared with the pre-existing three-drug regimens. Thus, captopril and nifedipine have been compared with hydralazine as third-line agents.²⁹ All three reduced blood pressure equally well when given in combination with the β -blocker/diuretic. In a subsequent study, the same group then went on to determine the relative contribution of the β -blocker to these regimens. Patients were randomised to withdrawal or continuation of atenolol from the two regimens, which included bendrofluzide/atenolol plus either captopril or nifedipine.³⁰ Results were disappointing, in that there was no real difference in the BP in either group, whether they continued on atenolol or not. There was a tendency, however, for BP control to deteriorate more when withdrawn from the diuretic/nifedipine group than the diuretic/ACE-I group.

There is only one study, to our knowledge, which has specifically compared the efficacy of different three-drug combinations, which did not include β -blocker/diuretic dual therapy in both groups. It is a small but well-designed, randomised, double-blind, placebo-controlled, crossover study, which compared the BP-lowering efficacy of a β -blocker *vs.* a thiazide diuretic as third-line treatment, where BP was not adequately controlled with an ACE-I/CCB combination.³¹ Following a month of treatment with each, the addition of a diuretic caused a significant fall in BP compared with placebo and a significantly greater fall in BP than the β -blocker. In this study, the β -blocker was not additive to the ACE-I/CCB combination. These findings would therefore support the rationale for addition of a thiazide diuretic to an ACE-I plus CCB combination as an effective BP-lowering strategy.

Other studies have simply set out to demonstrate BP-lowering efficacy of particular three-drug combinations, without comparison to other regimens, and they deserve a brief mention. One such study has examined the effects of sequential addition of ACE-I, CCB and thiazide diuretic in patients

with severe hypertension (supine DBP 115–135 mmHg), of whom 32 were black and 58 white.³² There was a significant reduction in BP with the sequential addition of a CCB to an ACE-I, with a thiazide as third-line agent. Interestingly, the majority required dual and triple therapy, (83% and 79%, respectively). In addition, an equal proportion of black (63%) and white (63%) patients required the maximum doses of all three agents in combination. In a larger multicentre study, candesartan was used as first-line therapy in individuals with moderate-to-severe essential hypertension.³³ Amlodipine was added as a second agent, where necessary, and then hydrochlorothiazide, to achieve a sitting DBP target of <90 mmHg. In patients whose DBP was maintained at <95 mmHg, there followed a period of randomised, placebo-controlled withdrawal of candesartan therapy. The results demonstrated a significant increase in BP in the groups where candesartan was withdrawn from the antihypertensive regimen, but not in the groups who continued to receive the active treatment. Thus the ARB, candesartan, was found to be an effective BP-lowering agent when given as monotherapy, in combination with amlodipine and in combination with amlodipine and hydrochlorothiazide.

Resistant hypertension and fourth-line agents

Resistant or refractory hypertension exists when the BP remains above the treatment target, despite treatment with a rational combination of three drugs, at adequate doses. If not addressed at the outset of treatment, then attention should be directed to lifestyle modifications, particularly dietary salt reduction, with a generally healthy eating plan based on the DASH³⁴ diet. A frank discussion regarding drug compliance and avoidance of exacerbating factors such as NSAIDs, which are frequently purchased over the counter, is also worthwhile. At this stage, a referral to a specialist unit is warranted for exclusion of secondary causes of hypertension.

Where BP is not controlled on three drugs, there is more of a difference in opinion as to which agent to add next. In general, personal experience with other agents dictates the choice of fourth-line agent, which is usually an α -blocker, β -blocker, loop diuretic or distally acting diuretic.

It is not clear from any objective study, which of these combinations is more efficacious, either in terms of BP-lowering or clinical outcome. A comparative study of α -blockers, β -blockers, loop and distally acting diuretics as fourth-line agents would be welcome.

Future considerations

Improvement in surrogate endpoints may be encouraging, but is not necessarily predictive of hard clinical endpoints. This has been shown in recent clinical trials (e.g. doxazosin in ALLHAT³⁵ and antioxidants in HOPE³⁶), where improvements in various markers did not result in improved cardiovascular outcomes. In addition, clinical trials in

highly selected sub-populations, as well as meta-analyses of pooled data, suggest that for equivalent BP-lowering, ACE-I are both cardioprotective and renoprotective,^{37,38} and ARB may be renoprotective,^{39,40} while CCBs may offer better protection from stroke.² When trying to assess the relative merits of different treatment strategies in hypertension, including different drug combinations, there will be no substitute for large randomised clinical outcome trials. In hypertension, the LIFE study is the first to demonstrate a convincing benefit of one drug combination over another and we await the results of the ASCOT study.

The fact remains that around 90% of UK hypertensives are inadequately controlled. This degree of under-achievement in healthcare provision is unacceptable. Certainly, we can improve on this standard of care. If the question is how, then one of the answers is to make use of rational drug combinations, which are more likely to lower BP, without intolerable side-effects. We have outlined a simple protocol in Figure 1 for the rational prescribing of antihypertensive drugs in combination.

Further considerations for encouraging the widespread use of combination drug regimens for hypertension might be to encourage the use of fixed-dose combination preparations. In addition, we may benefit from the return to a more didactic, stepped-care approach to prescribing. Thus, if BP has not fallen to target levels, the physician would proceed to the next rational line of therapy, as if following a protocol. This approach has been employed with great success in the large outcome trials, which set strict BP targets. Obviously, treatment algorithms would need to be carefully designed, according to the prevailing evidence-base and should be fully endorsed by the relevant societies involved in the drawing-up of guidelines. These approaches will not guarantee success in every case, but may help us to achieve target BP in a greater proportion of our patients.

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