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ORIGINAL ARTICLE

Better blood pressure control: how to combine drugs

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Prospective comparisons of different drug classes have shown that differences in blood pressure control, rather than differences between drug classes, have the overriding influence on overall outcome. The same studies have also reinforced the need, in the majority of patients, to use combinations of drugs in order to achieve the target of <140/85 mmHg. By contrast, most patients in routine practice receive single agents and consequently fail to achieve target blood pressure. This failure reflects in part the emphasis in individual studies and subsequent guidelines on comparison of individual drugs. In this article we show how the consistency of both theory and a broad range of evidence permits a didactic approach to combination therapy. Our advice is based on the growing recognition that essential hypertension and its treatment fall into two main categories. Younger Caucasians usually have renin-dependent hypertension that responds well to angiotensin-converting-enzyme inhibition or angiotensin receptor blockade (A) or ß blockade (B). Most other patients have low-renin hypertension that responds better to calcium channel blockade (C) or diuretics (D). These latter drugs activate the renin system rendering patients responsive to the addition of renin suppressive therapy. Coincidence of the initials of these main drug classes with the first four letters of the alphabet permits an AB/CD rule, according to which recommended combinations are one drug from each of the 'AB' and 'CD' categories of drugs. However, the diabetogenic potential of the older 'B' and 'D' classes leads us to advise against combining 'B' and 'D' in older patients, and to recommend 'A' + 'C' + 'D' as standard triple therapy for resistant hypertension.
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Introduction

This review is prompted by the gap between what is ideal, recommended and possible, and what is actually practised in the management of hypertension. It describes the importance and practicalities of bridging this gap. Overall, hypertension trials and their meta-analysis have emphasized that good blood pressure control is of paramount importance in ensuring optimal prevention of adverse cardiovascular events, such as strokes and myocardial infarctions. We briefly review the evidence for this conclusion, and then elaborate a scheme for achieving blood pressure targets. The emphasis of the review is on the need for combination therapy in the majority of patients. The previous emphasis on selecting a first-line agent from the large choice of drugs and classes available in hypertension is now inappropriate, given that current evidence is consistent in showing that the majority of patients require two or more agents to reach currently recommended blood pressure targets. Here, we provide two simple alternative treatment algorithms based on the fact that most drugs can be allocated into one of two main types: those that lower blood pressure by suppressing the renin system, and those that cause reflex activation of renin while lowering blood pressure in a different way. Effective combinations are likely to use one of each drug type.

Methods (Box 1)

Comments on the estimated morbidity associated with hypertension in the future are based on the World Health Organization (WHO) Global Burden of Disease study,[1] and a number of long-term epidemiological studies incorporated into the MacMahon *et al* meta-analysis.[2] The meta-analysis of hypertension outcome trials produced by the Blood Pressure Lowering Treatment Trialists Collaboration,[3] and

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Box 1 Recommendations

1. In younger nonblack patients either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (A) or in some circumstances β-blockers (B) should be used as an initial therapy. In older or black patients calcium channel blockers (C) or diuretics (D) should be used initially.
2. The majority of patients need a combination of drugs in order to achieve a blood pressure target of 140/85 mmHg (140/80 mmHg in diabetics).
3. When two drugs are needed, A (or B) should be combined with C or D, and for triple therapy A+C+D should be used.
4. We encourage use of a clear treatment plan in which initial and target blood pressure is noted by the doctor/nurse for the patient at the outset, together with expected treatment titrations.
5. Adherence to the plan includes continued documentation of blood pressure, ideally by the patient for the doctor/nurse.
6. We encourage, given specified conditions, prescribing of fixed dose combinations of optimal drugs in order to improve concordance with multiple drug therapy.

some of the individual constituents, informs most of the discussion about long-term benefits of treatment. Crossover studies of drugs within the same patient have, in particular, supported the division of drug responses into those that either suppress or activate the renin system. This forms the basis of the selection of the first-line drug class.

Thereafter, our suggested treatment plan is less evidence-based because of the paucity of studies comparing combinations of drugs. We have not deviated, except perhaps in detail, from the advice in several national and international guidelines.[4–6] However, we have drawn on the extensive literature concerning the pathogenetic mechanisms of hypertension, together with a number of multiple drug comparisons within the same trial, in order to rationalize recommended combinations.

Prevalence and morbidity of hypertension

Hypertension is one of the common causes of the global disease burden.[1] This situation is likely to worsen rather than improve, given an ageing world population increasingly exposed to the major environmental determinants of raised blood pressure. Of the six major contributors to global disease burden listed by Murray and Lopez,[1] only hypertension is amenable to drug treatment. Fortunately, some of the best evidence for the primary prevention of cardiovascular diseases is that provided by over 25 major randomized controlled trials, which have demonstrated the efficacy of lowering high blood pressure to prevent fatal and nonfatal strokes, and coronary heart disease events. Despite this, there is a large and unacceptable gap in blood pressure control between what is currently recommended based on the trial evidence, and what is achieved—particularly in the UK. In the most recently reported data from the 1998 Health Survey for England, only 39% of hypertensive adults were controlled to the old British Hypertension Society (BHS) target of 160/95 mmHg and less than 10% to the newer target of 140/85 mmHg.[7] Hence, 90 out of every 100 patients with hypertension have inadequately controlled blood pressure. Although these findings represent an improvement in hypertension management since the 1960s and have even improved since 1994,[8] further major improvements are required in order to reverse the component of stroke and coronary heart disease risk attributable to raised blood pressure.

One major mechanism whereby blood pressure control could be improved is by the increased use of more than one antihypertensive agent. As of 1998, the Health Survey for England data show that the majority (60%) of those on treatment for hypertension received one agent only, and a small minority (7%) were on three or more agents. These findings were unchanged from 1994.[7,8]

Importance of good blood pressure control and the need for combination treatment to achieve targets

One of the most important findings of the meta-analyses of the blood pressure lowering trials was the confirmation that patients randomized to more rather than less intensive treatment have a 20% lower rate of strokes and coronary heart disease events.[3] Consistent with these outcome trials data are observational data, which show that the achieved blood pressure is a major determinant of outcome.[9] To date, the only trial specifically designed to investigate optimal blood pressure targets was the Hypertension Optimum Treatment (HOT) trial, which was designed to evaluate whether $\leqslant 90$, $\leqslant 85$, or $\leqslant 80$ mmHg was optimal. However, the achieved blood pressure differences (4 mmHg) fell short of the 10 mmHg spread intended,[10] and so the study was underpowered to provide definitive evidence of the optimal target. Nevertheless, the trial was valuable in demonstrating the need for and success of combination therapy (used in 70% of patients) in controlling blood pressure to $<140/90$ mmHg. The United Kingdom Prospective Diabetes Study (UKPDS) also found a substantial improvement in outcome in patients randomized to tighter blood pressure control, irrespective of the treatment used.[11] As in HOT, almost 70% of patients in UKPDS required more than one drug to achieve a tighter control of blood pressure, and 24% received three drugs. In the more severe hypertensive patients recruited to the Losartan Intervention For Endpoint reduction (LIFE) trial, 90% of patients required two or more agents to reach mean blood pressure levels of 145/81 mmHg.[12] Even these figures exaggerate the success of monotherapy because they do not take account of patients either failing to achieve target or dropping out of the study.

The International Nifedipine Study (INSIGHT) achieved the best blood pressure control in recent hypertension outcome trials with an average of 138/82 mmHg; however, only 70% of all patients finishing the study achieved a target blood pressure $\leqslant$140/85 mmHg, and only 50% of patients were at target on one drug.[13] Since 30% of patients failed to complete the study, and had higher blood pressures than the study average when last measured, it can be calculated that even within a trial environment the odds against initial treatment achieving goal blood pressure were two in three; for patients with diabetes in INSIGHT, these odds rose to three out of four (Brown, unpublished).

Despite these *ad hoc* additions of second drugs in a large proportion of patients, the emphasis in evidence-based guidelines has been towards advice on initial, single treatments.[4,6,14] In the light of the evidence presented above, we now appreciate the futility in most patients of trying to reach current blood pressure targets with a single drug, and the evidence base is strongly in favour of combining drugs to achieve blood pressure goals. There are branches of medicine such as oncology where, in order to block the multiple processes known to contribute to the disease, combination treatment is the norm. The exact mechanisms accounting for the elevation of blood pressure in essential hyper-tension remain unclear, but the physiology of the control of blood pressure through the interaction between sodium balance and the renin–angiotensin system is well understood.

Summary of current BHS guidelines re: thresholds, targets and drug classes

Box 2 summarizes the current advice from the BHS regarding blood pressure thresholds and targets for treatment. Our website and publication contain more detailed diagrams together with the main indications/contraindications for each drug class. The advice is helpful to tailoring therapy to the profile of individual patients with coexistent morbidities. Here we offer an additional, simple algorithm for both initial drug treatment in the asymptomatic patient, and the subsequent additions likely to be required (Figure 1).

Box 2 Cutoffs and targets for antihypertensive treatment

- Treat if blood pressure $\geqslant$160/100 mmHg or ($\geqslant$140/90 mmHg+other CV risk or target organ damage)
- Reduce blood pressure to $<$140 and $<$85 mmHg, and lower for patients with diabetes
- This extrapolation to lower blood pressure should probably also apply to other groups at high cardiovascular risk (eg poststroke, renal disease)

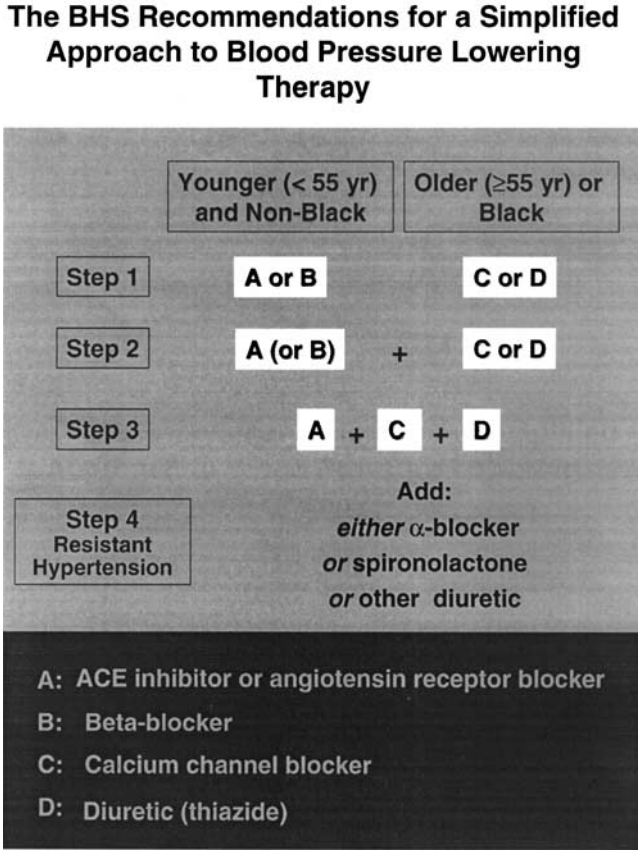

Figure 1 Modified Cambridge AB/CD Rule. Initial monotherapy (step 1) is selected according to age and ethnic group, as surrogates for plasma renin. In step 2, one drug from each of the AB and CD categories combined. Because of the diabetogenic potential of the older classses in older patients, B is shown in parenthesis at step 2, and is dropped altogether from step 3 (triple therapy). Recommendations for step 4 (quadruple therapy) are more anecdotal and may require secondary referral. Non-thiazide diuretic therapy is most appropriate in patients with normal renal function and suppression of plasma renin despite receiving the A+C+D combination.

Rationale for drug classes used

First-line therapy

The main classes of blood-pressure-lowering drugs can be grouped into two categories. The first comprises drugs that inhibit or block the renin–angiotensin system, namely angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and β-blockers. The second category comprises drugs that lower blood pressure independent of the renin–angiotensin system, and indeed cause reflex activation of this system. The calcium antagonists are primarily vasodilators, with a weak natriuretic action, whereas the reverse is true of thiazide diuretics. Younger white hypertensive patients tend to have higher levels of renin and angiotensin II, and available evidence points to starting such patients on a drug that inhibits the renin–angiotensin system for optimal blood pressure lowering.[15–18] However, such drugs are less

effective in patients with low renin hypertension, namely most patients of African origin and older patients; it is therefore sensible to start with either a diuretic or calcium antagonist for these patients.[18] In hypertension terms, the transition from younger to older seems to occur between 50 and 60 years old. This observation is based on changes in average plasma renin during this decade,[19] on inspection of age ranges in the trials that report age-related differences in blood pressure response to drugs,[16–18,20] and on the greater success to date of category 1 than category 2 monotherapy in the double-blind outcome trials conducted in the over 55–80 age group.[12,13]

Changes in treatment depend on the efficacy and tolerability of the first drug. If this is clearly ineffective (eg fall in systolic BP <5 mmHg), then the patient should be switched from one to the other category (eg from ACE inhibition to diuretic). Larger falls could still represent a placebo response, but the emphasis we are now giving to combination treatment encourages greater use of add-on therapy rather than switching, on the basis that complementary drugs help each other to work even when individually their efficacy is poor. If, therefore, the blood pressure falls but is not controlled, then a drug should be added from the other category. This will have a complementary action on the renin–angiotensin system.[21,22] On the other hand, a patient who responds to, but does not tolerate, a drug should change to the other drug within the same category (eg from β-blocker to ACE inhibitor).

Add-on therapy

Few published data are available to guide which combination of antihypertensive agents should be used. Pending good trial evidence such as that likely to arise from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),[23] we reiterate the BHS guideline recommendations regarding optimal treatment combinations.[4] These are outlined in Figure 1, which encapsulates a modified version of the Cambridge 'AB/CD' rule.[16] The results of the LIFE trial, particularly the 9% risk of new diabetes in patients receiving β-blockade and diuretics, will probably lead to a trend away from combining the two cheapest but potentially diabetogenic drug classes.[12,24] Therefore, we can simplify the AB/CD recommendations by suggesting that in older patients A (either an ACE inhibitor or angiotensin blocker) is added to the initial therapy with C or D.

If a two-drug combination does not control blood pressure, a third drug should be added. Once again, comparative data to guide practice in this regard is lacking. Nevertheless, treatment-resistant patients (especially diabetics) are often those where blood pressure control is particularly important. Evidence-based advice is superior to either anecdote- or theory-based advice, but the latter is probably superior to offering no advice at all. Once the renin system is inhibited, a diuretic is additive to a calcium antagonist. Therefore, triple therapy should consist of A+C+D. There are two reasons for our recommendation that, in the absence of a relevant comorbidity such as angina, β-blockade be omitted from the initial triple therapy. The first is our concerns, above, about combining B+D. The second is that in patients uncontrolled despite triple therapy, a plasma renin off β-blockade (which suppresses renin) should be measured as part of a reconsideration of secondary causes of hypertension. Primary hyperaldosteronism, defined as an elevated plasma aldosterone-to-renin ratio and blood pressure responsive to spironolactone, will be present in 5–10% of such patients.[25,26] In other patients, addition of an α-blocker may be effective. The last but usually successful resort is to the powerful vasodilator minoxidil. However, this requires careful titration, in combination with a β-blocker and loop diuretic, and leads to hirsutism and coarsening of facial features. Some specialists would therefore first try additional diuretics before proceeding to minoxidil. Others would try atypical combinations, such as β-blockade+ARB ($\pm$ ACE inhibitor) to suppress the renin system in high-renin patients not controlled by maximal dose of ACE inhibitor, or spironolactone+ARB in order to take out the whole renin–angiotensin–aldosterone system.

Treatment plans and the use of fixed dose combinations

One reason for the poorer blood pressure control in everyday life compared to clinical trials is the lack of both a clear treatment plan and transparency over prespecified blood pressure targets. We would encourage a written treatment plan that sets out for each individual patient a clear blood pressure target and the likely need for the addition of a second or third drug. In this way, there is no perceived element of patient disappointment or physician failure, where one drug fails to control blood pressure. In the didactic spirit of this article, we see provision of the plan as more important than its precise contents. Ideally, where appropriate, patients should have a copy of their plan with a running record of clinic $\pm$ home blood pressure readings. In most patients, particularly older and high-risk patients, the expectation must be for combination therapy.

One problem with an increased emphasis on the need for more than one drug class to control blood pressure is the number of tablets that patients need to take, making concordance an issue. Once control is achieved, we would now encourage the use of combination formulations. Providing that the cost of the combination is no greater than the component parts, the NHS as well as the patient gain financially. Hitherto an obstacle to achieving blood

pressure targets in the UK may have been our resistance based on theoretical arguments to the use of fixed-dose combination formulations. This is in contrast to the picture on much of the continent where such combination formulations are common and—whether coincidence or not—the percentage of patients with well-controlled blood pressure is much higher than in the UK.[27] Combination formulations of the pairs of drugs recommended above are now available. Previous specialist advice that these combinations magnify the risk of adverse events has been overtaken by good evidence to the contrary.[28] Nor need we be concerned these days with constituent drugs having different durations of action, since there is rarely need to use other than once daily drugs.

Primacy of drug combinations when using antihypertensive drugs

We have commented in this article on the gap between recommendations and practice. We are unlikely to see randomized outcome comparisons of single and combination treatment because monotherapy does not work for the majority of treated patients. Can we then reconcile the evidence for possible non-blood-pressure-lowering benefits from renin blockade in high-risk patients with our recommendations to start treatment with a calcium blocker or diuretic in older patients.[29] Whether 'add-on' benefit because of ACE inhibition is present in high-risk patients, independent of blood pressure lowering, remains controversial.[30–32] If such benefit exists, it is more evident when an ACE inhibitor is added to other antihypertensive drugs, as in HOPE,[29] than when used as sole therapy.[33] Combination therapy may summate not only blood pressure reductions of the individual drugs, but also the cause-specific benefits suggested by meta-analysis of the outcome trials.[3]

Conclusion

It is a tragic fact that 90% of patients with high blood pressure in the UK do not have their blood pressures adequately controlled to current targets, and hence many preventable strokes, heart attacks and cases of heart failure occur unnecessarily. It is our view that further action is now needed to achieve better control of blood pressure. This can, in the majority of patients, be easily achieved by the increased use of rational combination therapy.

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