Novel therapeutic concepts

Hypertension management 2011: optimal combination therapy

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Raised levels of blood pressure result from the complex interplay of environmental and genetic factors. The complexity of blood pressure control mechanisms has major implications for individual responsiveness to antihypertensive drugs. The underlying haemodynamic disorder in the majority of cases is a rise in peripheral vascular resistance. This observation led to the discovery and development of increasingly sophisticated and targeted vasodilators, although many of the earlier antihypertensive drugs, by virtue of their actions blocking the sympathetic nervous system, had a vasodilator component to their mode of action. A recent meta-analysis of placebo controlled trials of monotherapy in unselected hypertensives, reports average (placebo-corrected) blood pressure responses to single agents of 9.1 mmHg systolic and 5.5 mmHg diastolic pressure. These average values disguise the extremely wide ranging responses in individuals across a fall of 20–30 mmHg systolic at one extreme, to no effect at all, or even a small rise in blood pressure at the other. The second factor determining individual responses to monotherapy is the extent to which initial falls in pressure are opposed by reflex responses in counter regulatory mechanisms that are activated following the blood pressure reduction. Thus, a satisfactory blood pressure response is rarely reached with monotherapy alone. What then is the next step if blood pressure is not a goal after the patient has been treated with monotherapy for a few weeks? Should you uptitrate, substitute or combine?

Keywords
Hypertension • Combination therapy

Introduction

Raised levels of blood pressure result from the complex interplay of environmental and genetic factors leading to the activation or suppression of one or more of a host of physiological systems involved in blood pressure regulation (Figure 1). The complexity of blood pressure control mechanisms, first hypothesized by Irvine Page,1 has major implications for individual responsiveness to antihypertensive drugs (Figure 2), because of the inevitable variety of hypertensive phenotypes, the identification of which, with some notable exceptions, remains elusive to the practicing physician involved in making treatment decisions for individual patients.2

Hypertension is, by definition, a haemodynamic disorder. The major haemodynamic finding associated with higher levels of blood pressure is a rise in peripheral vascular resistance. This observation led to the discovery and development of increasingly sophisticated and targeted vasodilators, although many of the earlier antihypertensive drugs, by virtue of their actions blocking the sympathetic nervous system, had a vasodilator component to their mode of action. The first non-specific vasodilator, hydralazine, was followed by vasodilatation which involved blockade of calcium channels on vascular smooth muscle cells [the calcium channel blockers (CCBs)], blockade of post-synaptic alpha-adrenoceptors on peripheral sympathetic neurones (the alpha blockers) and, finally, vasodilatation achieved by blockade of the renin–angiotensin–aldosterone system (RAAS) [angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), direct renin inhibitors (DRIs)] (Figure 3).

The nature of these molecules, and in most cases their single site of action, dictates that when administered to a heterogeneous population, encompassing many hypertensive phenotypes, blood pressure responses will be largely unpredictable and wide ranging (Figure 4). If, in a particular case, blood pressure levels are largely determined by activation of the RAAS, for example in renal artery stenosis, marked falls in blood pressure with

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impairment of renal function may follow the administration of an ACE-Inhibitor. On the other hand, in the elderly and in those of African origins, where the activity of the RAAS is generally suppressed, blood pressure reductions with an ACE-Inhibitor may be small. In general, however, the phenotype is not known.

A recent meta-analysis of placebo-controlled trials of monotherapy, in unselected hypertensives, reports average (placebo corrected) blood pressure responses to single agents of 9.1 mmHg systolic and 5.5 mmHg diastolic pressure. These average values disguise the extremely wide ranging responses in individuals across a fall of 20–30 mmHg systolic at one extreme, to no effect at all, or even a small rise in blood pressure at the other (Figure 4).

The second factor determining individual responses to monotherapy is the extent to which initial falls in pressure are opposed by reflex responses in counter regulatory mechanisms that are activated following the blood pressure reduction. In
extreme cases, these reflex responses can nullify any fall in pressure (Figure 5).

Thus, a satisfactory blood pressure response is rarely reached with monotherapy alone. What then is the next step if blood pressure is not at goal after the patient has been treated with monotherapy for a few weeks? Should you uptitrate, substitute, or combine?

Uptitration

Uptitration of the initial drug is reasonable only if definitive, enhanced antihypertensive efficacy of the higher dose has been documented and the cost is not prohibitive. Regrettably, most antihypertensive drugs have a rather shallow dose–response curve. In particular, with RAAS inhibitors doubling the dose has minimal incremental effect on blood pressure. In contrast, with CCBs, additional antihypertensive efficacy can be gained when, for example, the starting dose of amlodipine is doubled from 5 to 10 mg. However, the incidence of pedal oedema also is dose dependent and increases with a higher dose of amlodipine. Importantly, the additional blood pressure fall from combining drugs from two different classes is ≈5 times greater than the one from doubling the dose of a single drug. Thus, the odds of getting blood pressure to goal are several times greater with combining drugs than with up titration of monotherapy. From a sheer efficacy point of view, combination therefore takes precedence over uptitration.
Substituting an antihypertensive drug from a different class should be considered only if there is no antihypertensive effect with a reasonable dose, as is occasionally observed with beta-blockers or RAAS blockers in black patients, or if there are any intolerable adverse effects such as angioedema. Fortunately, most modern antihypertensive drugs are generally well tolerated and serious adverse effects are few. However, before resorting to drug substitution one may consider that the addition of another drug may unmask the antihypertensive efficacy of the initial agent. For instance, the addition of a thiazide diuretic in a patient previously unresponsive to RAAS blockade is prone to stimulate the renin–angiotensin system to the extent that now both drugs, the RAAS inhibitor as well as the diuretic, have an additive antihypertensive effect.

Rationale for combination therapy

The rationale for combination therapy in hypertension is therefore straightforward. First, it is to combine drugs acting on different physiological systems in a situation where the phenotype is not known and where a pharmacological ‘attack’ on two (or more) systems will have a greater impact on blood pressure reduction than blind monotherapy. Second, it is an attempt to block counter-regulatory responses that are activated by the perturbation of the blood pressure regulatory mechanisms when a physiological system is blocked with single-drug therapy (Figure 6).

Third, the hypertensive population includes many with levels of blood pressure categorized as moderate or severe (stage 2 hypertension). There is general consensus that those with systolic blood pressures >160 mmHg and/or diastolic pressures >100 mmHg fall into this category. They constitute 10–15% of hypertensive populations and are at substantially greater risk of a future cardiovascular event. For every 20 mmHg increase in systolic blood pressure, there is an approximate doubling of cardiovascular risk.

Obviously the proportion of the population with hypertension increases with age and this also applies to those with stage 2 hypertension. As age advances systolic hypertension predominates and is largely accounted for by loss of elasticity and increasing rigidity of large arteries.

![Compensatory mechanisms of action of CCBs, diuretics and RAAS-blockers on vascular and renal function, SNS activity and RAS activity](image)

Although there are some differences between guidelines, several now recommend the initiation of combination therapy as first line in particular circumstances, in view of the associated risks of more severe hypertension, the recognition that dual (or triple) therapy is invariably needed to achieve target blood pressures of <140/90 mmHg, and that there is a degree of urgency in reducing blood pressure to more acceptable levels to combat this risk.

JNC-7 recommends initiating therapy with two drugs when blood pressure is >20 mmHg above systolic goal or 10 mmHg above diastolic goal. The European Guidelines, including their most recent update, confirm such a recommendation and also propose the initiation of combination therapy in those with milder degrees of blood pressure elevation in the presence of multiple risk factors, subclinical organ damage, diabetes, renal, or associated cardiovascular disease. Although combination therapy is not specifically advocated as initial therapy in the 2004 British Hypertension Society Guidelines (largely based on the fact that there is a lack of randomized controlled trial evidence to support such practice), it is probable that the results of ongoing trials will provide new evidence in favour of their early introduction into treatment strategies.

Inevitably, there are concerns that initiating therapy with more than one drug could induce significant hypotension and increase coronary risk. An analysis of intervention trials in hypertension provides some evidence for a ‘J-curve’ relationship between the magnitude of blood pressure lowering and coronary heart disease outcome, but this seems to be confined to high-risk individuals including those with established coronary artery disease, in whom excessive blood pressure lowering compromises coronary perfusion. In uncomplicated hypertension, lower pressures are well tolerated, for example, as seen in the Systolic Hypertension in the Elderly Study, in which diastolic pressures as low as 60 mmHg were achieved in the active treatment group. Ongoing trials comparing initiation of dual therapy vs. sequential monotherapy in hypertension will aim to clarify the safety of the former.

Fourth, blood pressure variability has been shown to decrease with combination therapy when compared with monotherapy. In an extensive analysis of several randomized trials, visit-to-visit variability of systolic blood pressure was documented to be a strong predictor of both stroke and myocardial infarction and this was independent of mean in-trial blood pressure. Interestingly enough, CCBs and diuretics were most efficacious in reducing visit-to-visit blood pressure variability and also were associated with the most efficacious stroke prevention. In contrast, beta-blockers were shown to increase variability of systolic pressure in a dose-dependent way and also were the least efficacious in stroke prevention. The addition of a CCB or to a lesser extent of a diuretic to a RAAS inhibitor diminishes variability of systolic pressure, which makes another strong argument for combination therapy.

Trial evidence for and against specific combinations

An extensive review of first-line drug choices has been published by the Blood Pressure Lowering Treatment Trialists’
Collaboration and is based upon prospective meta-analyses of trials comparing different drug regimens. Similar analyses have been undertaken by the National Institute for Clinical Excellence (NICE) in the UK. The difficulty in extending these analyses to evaluate the comparative effects of different combinations of drugs is that in many trials it is not possible to establish which add-on drugs were used and in what doses. The evidence base for making claims about the comparable or superior efficacy of one regimen vs. another comes from trials where the treatment algorithm was clearly defined and one could conclude with reasonable assuredness that a particular regimen was similar to, better than or worse than another. The best evidence, from which claims can be made of outcomes in favour of a particular regimen, comes from four trials, the Losartan Intervention For Event Reduction Trial (the LIFE Trial), the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension Trial (ACCOMPLISH) and the Valsartan Antihypertensive Long-term Use Evaluation Trial (VALUE).

In the LIFE Trial, 9193 hypertensive patients were randomized to initial treatment with either an ARB (losartan) or a beta-blocker (atenolol). Hydrochlorothiazide was added in the majority of patients to achieve blood pressure control, along with the further addition of common third-line agents in a minority of patients. After an average follow-up of 5 years during which there was no discernable difference in blood pressure between the two regimens, the composite primary cardiovascular endpoint was reduced by 13% in the losartan-based group compared with the atenolol-based group. The major benefit was seen in the secondary stroke endpoint (a component of the primary) which was reduced by 25% in the losartan-based group.

In the second trial, ASCOT, over 19,000 hypertensive patients with no prior history of coronary heart disease were randomized to either a CCB, amlodipine, or a beta-blocker, atenolol. The ACE-Inhibitor perindopril or the diuretic bendroflumethiazide was added to each arm, respectively, in an attempt to achieve blood pressure targets. Again, common third-line drugs could be added to each arm in a minority of patients. After an average follow-up of 5.5 years, the trial was stopped prematurely on the advice of the Data Safety Monitoring Committee, because of highly significant outcome benefits in favour of the amlodipine-based regimen. All cardiovascular events were reduced by 26%, stroke by 23%, and all-cause mortality by 11% by the amlodipine-based regimen compared with the atenolol-based regimen. The primary endpoint of non-fatal myocardial infarction and fatal coronary disease was reduced non-significantly by 10% in favour of the amlodipine-based regimen, best explained by the early termination of the trial before the required number of primary endpoints had been reached. In the event, a more comprehensive coronary endpoint which included coronary revascularizations was reduced significantly by 13%.

In several subsequent analyses, the small blood pressure differences observed early in the trial did not explain the outcome benefits in favour of amlodipine-based treatment. In recent reports, however, it has been shown that additional haemodynamic measurements may be better determinants of cardiovascular outcome, and differentially affected by different treatment strategies. For example, in the CAFÉ substudy of ASCOT, the amlodipine/perindopril regimen lowered central aortic blood pressure to a greater extent than the atenolol/thiazide regimen (by 4 mmHg systolic), and the level of central pressure was related to cardiovascular and renal outcomes. In another substudy, various measures of blood pressure variability during the trial were strongly associated with both stroke and coronary outcomes, in that the amlodipine-based treatment regimen reduced blood pressure variability compared with the atenolol-based regimen. These differences largely accounted for the observed differences in cardiovascular outcomes between the two-drug regimens.

In the third trial, ACCOMPLISH, 11,506 hypertensive patients were randomized to a combination of the ACE-Inhibitor, benazepril, with either hydrochlorothiazide, or the CCB, amlodipine. Patients were followed for 3 years. Blood pressure levels were reduced similarly in the two arms of the trial. Cardiovascular events were significantly reduced by 20% in benazepril/amlodipine arm compared with the benazepril/hydrochlorothiazide arm. Myocardial infarction was reduced significantly (22%) and stroke non-significantly (16%) by benazepril/amlodipine compared with benazepril/hydrochlorothiazide. The benefits of the benazepril/amlodipine combination over benazepril/hydrochlorothiazide were seen in both diabetic and non-diabetic patients.

In the fourth study, VALUE, 15,245 hypertensive patients were randomized to either the ARB, valsartan, or the CCB, amlodipine. Hydrochlorothiazide was added to each limb in attempting to achieve goal blood pressures. Other add-on drugs were similar in the two treatment arms. Mean follow-up was 4.2 years. Blood pressures were more effectively and more rapidly reduced in the amlodipine-based treatment arm. Although the primary composite endpoint of cardiac morbidity and mortality was similar in the two arms of the trial, myocardial infarction occurred significantly less frequently (risk reduction 19%) and strokes non-significantly less often (risk reduction 15%) in the amlodipine-based treatment arm compared with the valsartan-based arm. The authors of the trial attributed early differences in blood pressure as an explanation for the differential effects of the two treatments on myocardial infarction and stroke.

The cumulative evidence from these trials strongly supports the view that, in hypertensive patients, combination therapy with CCB/ACE-I or CCB/ARB is likely to be associated with better cardiovascular outcomes, including myocardial infarction and stroke, than regimens containing beta-blockers and thiazide diuretics and that CCB/ACE-I combinations are preferable to diuretic/ACE-I combinations on major cardiovascular endpoints. Added to this should be the cost-effectiveness analysis from the NICE Guidelines which clearly demonstrates that CCBs and ACE-Is or ARBs are more cost-effective treatment choices than beta-blockers or thiazide diuretics.

The above recommendations apply, in general, to those subjects with uncomplicated hypertension. In hypertensives with associated cardiovascular disease such as heart failure or coronary heart disease, the guidelines are consistent in recommending specific drugs with compelling indications, based on randomized controlled
Specific drug combinations

Given that there are seven major classes of antihypertensive drugs and numerous members of each class, the number of possible combinations is extensive. In the following, we subdivide combinations as preferred, acceptable or unacceptable/ineffective combinations, based on outcome, antihypertensive efficacy, safety, and/or tolerability.

Preferred combinations

Renin–angiotensin–aldosterone system inhibitors and calcium channel blockers

Additive blood pressure reduction has been documented with the combination of an ACE-Inhibitor, ARB, or DRI with a CCB. The common dose-dependent adverse effect of CCB monotherapy is peripheral oedema. The addition of a RAAS blocker has been shown to mitigate this adverse effect. A recent meta-analysis has shown that ACE-Inhibitors are somewhat more efficacious than ARBs in decreasing peripheral oedema associated with CCB therapy. General, similar end-point reductions have been demonstrated with ACE-Inhibitors and ARBs, although there is a suggestion that ACE-Inhibitors may be slightly more cardioprotective and that ARBs may confer some advantages in stroke prevention.

The International Verapamil-Trandolapril Study (INVEST) was a comparison of ‘new’ vs. ‘old’ drugs in that a regimen of the none dihydropyridine, verapamil, to which trandolapril was added if necessary, was compared with atenolol to which hydrochlorothiazide was added if necessary to achieve blood pressure goals. A total of 22,576 hypertensives with established coronary artery disease were enrolled and followed up for a mean of 2.7 years. The combined cardiovascular outcome was similar in the two groups. Perhaps the most logical explanation for these findings is that the disadvantage of the beta-blocker regimen observed in hypertension trials in uncomplicated patients was offset by the known advantages of beta blockade in the context of established coronary artery disease.

Renin–angiotensin–aldosterone system inhibitors and diuretics

Numerous factorial design studies have shown that the combination of a thiazide diuretic with an ACE-Inhibitor, an ARB, or a DRI result in fully additive blood pressure reduction. Diuretics, by depleting intravascular volume, activate the RAAS which causes salt and water retention as well as vasoconstriction. The addition of a RAAS blocker attenuates this counter regulatory response. Moreover, diuretic induced hypokalaemia as well as glucose intolerance is mitigated by the addition of a RAAS blocker. Chlorothalidone has been shown to be more effective than hydrochlorothiazide in reducing blood pressure and should therefore be the preferred agent to be combined with a RAAS blocker. Unfortunately most RAAS inhibitors are available only in a fixed-dose combination (FDC) with hydrochlorothiazide.

In a recently reported study in a very elderly (>80 years) hypertensive population, the Hypertension in the Very Elderly Study (HYVET), a thiazide-like diuretic, indapamide, to which an ACE-Inhibitor, perindopril, was added, was found to reduce stroke incidence (30%) and the incidence of heart failure (64%), compared with placebo.

Acceptable combinations

Beta-blockers and diuretics

The addition of diuretics has been shown to improve the antihypertensive efficacy of beta-blockers in African-American patients and other populations with low-renin hypertension. However, both of these drug classes have been shown to have similar adverse effects in that they increase the risk of glucose intolerance, the development of new-onset diabetes, fatigue, and sexual dysfunction. Outcome studies have shown a morbidity and mortality reduction with diuretics and beta-blockers in combination.

Calcium channel blockers and diuretics

Most physicians are somewhat reluctant to combine a CCB with a diuretic. However, in the VALUE trial, hydrochlorothiazide was added as a second step in patients randomized to amlopidine and the diuretic/CCB combination was well tolerated, although there was a higher risk of new onset diabetes and hyperkalaemia when compared with the valsartan arm. Nevertheless, morbidity and mortality reductions were at least as good in the amlopidine as in the valsartan arm of the VALUE study.

Calcium channel blockers and beta-blockers

The combination of a beta-blocker with a dihydropyridine CCB has additive blood pressure reduction and, in general, is well tolerated. In contrast, beta-blockers should not be combined with non-dihydropyridine calcium blockers such as verapamil or diltiazem. The negative chronotropic effect of both of these drugs may result in heart block or bradycardia.

Dual calcium channel blockade

The combination of a dihydropyridine CCB with either verapamil or diltiazem has been shown in a recent meta-analysis to have an additive effect on blood pressure lowering without significantly increasing adverse events. Dual CCB blockade may be useful in patients with documented angioedema on RAAS inhibitors or in patients with advanced renal failure at risk for hyperkalaemia. However, no outcome data are available with dual CCB therapy and long-term safety remains undocumented.

Unacceptable/ineffective combinations

Dual renin–angiotensin–aldosterone system blockade

For the treatment of hypertension per se, dual RAAS blockade, in general, is not recommended. In the ONTARGET study, there were more adverse events with a combination of telmisartan and ramipril than with individual agents and cardiovascular endpoints, despite a small additional blood pressure reduction, were not improved compared with monotherapy. Thus, there is little if any...
reason to combine an ARB with an ACE-Inhibitor for the treatment of hypertension. However, as blockade of the renin–angiotensin cascade by either an ACE-Inhibitor or an ARB increases plasma renin activity, the argument has been put forward that the addition of a DRI could have additional benefits. Indeed, the combination of aliskiren with an ARB has been shown to have a small, significant additional effect on blood pressure in a double-blind study of 1797 patients. However, this fall in blood pressure with dual RAAS blockade was less than one would have expected by the addition of either a thiazide diuretic or a CCB. Of note, in an open label prospective crossover study in patients with resistant hypertension, the aldosterone antagonist spironolactone was shown to lower blood pressure more effectively than conventional dual RAAS blockade. At the present time, no outcome data are available to support benefits of the combination of a DRI with either an ACE-Inhibitor or an ARB. Nevertheless, a randomized double-blind trial (ALTI-TUDE) has been designed to look into this question and is currently in progress.

**Renin–angiotensin–aldosterone system blockers and beta-blockers**

In patients having suffered a myocardial infarction or in those in heart failure, these two drug classes are commonly combined because both have been shown to reduce reinfarction rates and to improve survival. However, their combination produces little additional blood pressure reduction compared with either monotherapy. Thus, for the treatment of blood pressure *per se*, there is no reason to combine these two drug classes.

**Beta-blockers and antiadrenergic drugs**

Little if any antihypertensive efficacy can be gained when beta-blockers are combined with antiadrenergic drugs such as clonidine. In fact, an exaggerated rebound in BP has been observed with this combination.

**Other drug classes in combination therapy: alpha-blockers and spironolactone**

Alpha-adrenoceptor antagonists have been widely used as add-on drugs in combination regimens to achieve target blood pressures. The availability of extended release formulations has improved their tolerability profile. Data from an observational analysis of the ASCOT trial showed that doxazosin gastrointestinal therapeutic system (GITS) used as third-line therapy lowered blood pressure and caused a modest reduction in serum lipids. In contrast to earlier findings in ALLHAT, doxazosin use in ASCOT was not associated with an increased incidence of heart failure.

For subjects with resistant hypertension, defined as failure to achieve target blood pressure (<140/90 mmHg) despite maximum doses or maximum tolerated doses of three antihypertensive drugs including a RAAS blocker, a CCB, and a thiazide diuretic, quadruple therapy is frequently required. Recent reports demonstrate that spironolactone added to triple therapy is associated with substantial further reductions in blood pressure of, on average, 22.9.5 mmHg. Spironolactone is therefore recommended as a component of combination therapy in patients with resistant hypertension.

**Adverse effects**

The adverse reactions associated with combination treatments are largely predicted from the known side effects of the individual components. However, in older combinations of vasodilators (hydralazine) with beta-blockers and diuretics, the side effects of vasodilatation (tachycardia and fluid retention) were mitigated by the additional drugs. There is some evidence that the oedema commonly associated with dihydropyridine CCBs is partially relieved by co-administration of RAAS blockers and RAAS blockers may reduce the incidence of hypokalaemia induced by thiazides. On the other hand, it seems likely that the increase in incidence of new-onset diabetes commonly associated with beta-blockers is exacerbated when these drugs are given in conjunction with thiazide diuretics. A meta-analysis of the increased incidence of new-onset diabetes with beta-blocker and thiazide treatment, compared with ‘newer’ drugs, is provided by the NICE Guidelines.

These conclusions assume that there are no differences between individual drugs within a particular drug class in relation to their effects on long-term morbidity and mortality. Among the CCBs, the best evidence is for amlodipine. Among the ACE-Is and ARBs, several different drugs have been used both within and without combination trials in hypertensive patients and in other cardiovascular patient groups, and no clear benefits of one drug over another are evident. For thiazide and thiazide-like diuretics, there persists an opinion that the evidence base for long-term benefits is best for moderate doses of chlorthalidone, compared with other thiazides in lower doses. Regrettably, there are unlikely to be future trials comparing drugs within this class.

For the beta-blockers, atenolol has been the drug most often used and claims have been made that had other drugs in this class been used in the trials then perhaps different results would have occurred. This is unlikely since the adverse effects of atenolol, observed in ASCOT, are unlikely to be future trials comparing drugs within this class. For the beta-blockers, atenolol has been the drug most often used and claims have been made that had other drugs in this class been used in the trials then perhaps different results would have occurred. This is unlikely since the adverse effects of atenolol, observed in ASCOT, are unlikely to be future trials comparing drugs within this class. For the beta-blockers, atenolol has been the drug most often used and claims have been made that had other drugs in this class been used in the trials then perhaps different results would have occurred. This is unlikely since the adverse effects of atenolol, observed in ASCOT, are unlikely to be future trials comparing drugs within this class.
differences in blood pressure if sustained long term would undoubtedly confer advantages on cardiovascular outcomes.

**Blood pressure control in practice**

Worldwide surveys of blood pressure control to targets recommended by national and international guidelines have consistently revealed that in clinical practice the conventional goal of a blood pressure <140/90 mmHg is reached by only a minority of patients. Data from several countries are shown in Figure 5. While there are several explanations for physicians failing to achieve target blood pressures, including poor compliance or concordance with drug taking by patients, white coat hypertension, undiagnosed secondary causes of hypertension, and true resistant hypertension, in the majority of cases therapeutic inertia on the part of the physician plays a major role. There is good evidence that when physicians are faced with patients on treatment for hypertension, but who have not reached goal blood pressures, they are reluctant to increase drug doses or initiate second- and third-line combination therapy.

The issues surrounding these observations are complex. Clearly lack of education and failure to appreciate the importance of lowering blood pressure to targets to prevent cardiovascular outcomes associated with uncontrolled blood pressure are important issues. The historical focus on diastolic pressure as the basis for initiation of therapy and as a treatment target is another. In practice, diastolic targets of <90 mmHg are far more commonly attained than systolic targets of <160 mmHg.

Lastly, and importantly, true therapeutic inertia—the reluctance to change medications when faced with a patient whose blood pressures remain above goals. Excuses such as the following example—‘It’s a little bit higher today (cold weather, rush to clinic, stress at work, domestic problems etc) but we will see what it’s like in a few weeks/months time’ are all too frequent. This major problem can be overcome (as we observe in trials) when physicians or nurses are obliged to follow goal directed treatment algorithms dictated by a trial protocol, and when ‘excuses’ cannot be made to avoid changes in medications when blood pressures are not at target.

An alternative scheme, practised in the UK since 2004, has been to remunerate doctors based on the extent to which they achieve a number of clinical targets, one of which is dictated by the proportion of their hypertensive patients whose blood pressures are lowered to an audit standard of <150/90 mmHg. This has contributed to improvements in the levels of blood pressure control in the population and has been accompanied by the increasing use of combination therapies.

**Conclusions**

The use of combinations of drugs in therapeutic practice is common place in contemporary medicine in a wide variety of disease categories, for example, in infectious disease, to cover multiple organisms and to overcome drug resistance; in respiratory illness such as chronic bronchitis or asthma to target multiple pathophysiological mechanisms of disease and in neurological conditions to interfere with different abnormalities of neurotransmitter function. In fact throughout medicine, combination therapy is often the norm rather than the exception. In hypertension, the underlying rationale for combination therapy is somewhat different. Since we do not know the cause of the blood pressure elevation, therapy is essentially blind and a shotgun approach may be more efficacious than targeted therapy. This is particularly true because monotherapy invariably triggers a variety of counter regulatory mechanisms which are mitigated by combination therapy. Thus, a strong case can be made for the early introduction of combination therapy and conceivably, the time will come when combination therapy in low doses will be the preferred option for first-line treatment in patients with hypertension.

**Take home message and recommendations**

(1) Many, if not most patients, need two or more drugs from different classes to achieve blood pressure control.

(2) Combination therapy should be initiated if the patient’s blood pressure is >20/10 mmHg above target level unless cardiovascular status is brittle.

(3) Preferred or acceptable two drug combinations should be used (Table 1).

(4) Whenever convenience and cost outweigh other considerations fixed-dose combinations rather than individual drugs should be used.

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### Table 1 Drug combinations in hypertension: recommendations

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