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Desirable Therapeutic Characteristics of an Optimal Antihypertensive Agent

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Abstract

Hypertension affects 65 million people in the US, and is a major cause of morbidity and mortality, but less than one-third of patients with hypertension are treated to goal blood pressure. Multiple factors have been cited, and include suboptimal adherence to treatment and lifestyle modifications, limited access to healthcare services, and the failure of health professionals to treat hypertension aggressively. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends a goal blood pressure of <140/90mm Hg for most patients and <130/80mm Hg for those with diabetes mellitus or chronic kidney disease. The 'ideal' antihypertensive agent would have a number of characteristics: (i) effective in lowering blood pressure to recommended goals; (ii) high efficacy as monotherapy; (iii) rapid onset of effect; (iv) convenient once-daily dose administration to maximise compliance; (v) sustained efficacy over 24 hours; (vi) response increases with higher doses (clear dose-response effect); and (vii) optimum tolerability profile. Although the ideal agent does not yet exist and will vary from patient to patient, drug development and new formulations have provided more options for clinicians and patients and certain drug classes appear to show promise because they possess many beneficial characteristics. Hypertension treatment needs to be tailored to individual patients' age, race, socioeconomic situation, concomitant conditions and family history. Physicians and other clinical providers have an important role to play in hypertension management, particularly by combining culturally sensitive patient care with aggressive treatment. Regular follow-up that is directed at achieving goal blood pressure, while monitoring the

patient for possible drug-related adverse effects, will help ensure and support adherence to treatment regimens. By supporting the integration of lifestyle changes into this plan, the clinician can further influence and have a positive impact on a patient's overall cardiovascular profile.

The aging of the US population is a phenomenon widely described in the popular and scientific press. In 2005, approximately 37 million individuals were >65 years of age. In 2050, this number is expected to increase to nearly 84 million. The expected burden of cardiovascular disease will also increase. It is projected that in 2050, the proportionate mortality rate due to cardiovascular disease will increase to 33%, whereas cancer mortality rates are expected to decline.[1] A meta-analysis of 1 million adults in 61 prospective studies has shown that, throughout middle and old age, blood pressure (BP) is strongly associated with cardiovascular mortality.[2] Consequently, one of the most common risk factors for cardiovascular mortality is uncontrolled hypertension. Nearly one in three of the US population are hypertensive[3] and are therefore considered to be at an increased risk for cardiovascular events, including myocardial infarction, heart failure, stroke and kidney disease.[4] An analysis of the NHANES (National Health and Nutrition Examination Survey) III data set completed in 2000 by Fields et al.[3] estimates that approximately 65 million Americans have hypertension. According to American Heart Association statistics, hypertension contributes to or is the primary cause of death in more than a quarter of a million individuals each year in the US.[4] Because of the expected increase in the numbers of patients who have cardiovascular disease and the prevalence of hypertension currently present in the population, clinical management of chronic hypertension requires a challenging new level of vigilance to prevent the progression of cardiovascular disease.

The primary goal of antihypertensive treatment is to reduce cardiovascular morbidity and mortality.[4] The Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Blood Pressure (JNC 7) recommends BP targets of <140/90mm Hg in the majority of patients with hypertension and <130/80mm Hg in those with diabetes mellitus or chronic kidney disease.[4]

Unfortunately, the prevalence of hypertension is increasing in the US. Data from NHANES show that only 58% of patients are receiving treatment and BP is being controlled in just 29% of these patients.[5] Further examination of these data reveals even more alarming trends for African American and Hispanic patients. Rates of hypertension prevalence, awareness and treatment for these groups are significantly more disconcerting than those of their White counterparts. However, among treated patients, control rates are almost identical (29%) for non-Hispanic Whites and African Americans, whereas in Hispanics only 17% are controlled to goal. These differences reinforce the ongoing problem of health disparities in the US, requiring increased commitment to enhance access to care for these vulnerable patients. Therefore, better treatments and prevention programmes are urgently required for all in the US.[5]

The reasons for poor BP control are multifactorial and include the failure of healthcare professionals to treat aggressively,[6,7] the medical community's acceptance of BP levels above goal BP,[6,7] and lack of awareness of hypertension among patients.[8] In addition, poor adherence to medication and lifestyle modifications may be responsible for inadequate BP control in a large percentage of patients with hypertension.[4] Because hypertension is often asymptomatic and treatment may be associated with undesirable side effects, the primary motivation for patients to adhere to their medication is the knowledge that they may be reducing their overall cardiovascular risk.

Patient adherence is a significant factor in achieving goal BP. A drug regimen that is highly efficacious, is easily integrated into patients' daily activities and confers few, if any, adverse effects

would seem to maximise the chances for strong patient adherence. The number of drug choices available to treat hypertension may seem overwhelming to clinicians – especially when they are looking for a simple drug regimen to which patients will be likely to adhere. In table I, a matrix is proposed that will assist clinicians when evaluating the range of therapeutic choices for antihypertensive therapy.

This framework and review of the salient features of the JNC 7 guidelines should help guide clinicians in identifying the 'optimal' antihypertensive drug regimen that will maximise the chances of their patients achieving goal BP and reducing their overall risk of cardiovascular disease.

1. JNC 7 Guidelines

Overall, there is a high level of agreement amongst US and European guidelines related to hypertension,[4] with some points of difference that are of only minor clinical significance.[9,10] On both continents, the guidelines emphasise the health risks associated with high BP, and highlight the benefits of reducing BP in relation to fatal and nonfatal cardiovascular outcomes. The most widely publicised of the current guidelines are the JNC guidelines, which were updated in 2003 and provide an evidence-based approach to the treatment of hypertension.[4]

Educating patients in the adoption of a healthy lifestyle is easy for clinicians to communicate but sometimes daunting for patients to adopt. These important cornerstones of treatment are emphasised prominently in US and European clinical guidelines related to hypertension.[4,9,11] The 'nonpharmacological' recommendations for behaviour change found in the JNC 7 guidelines include maintaining a healthy bodyweight, eating a diet rich in fruit and vegetables and low in sugar and fat (the Dietary Approaches to Stop Hypertension, or DASH, diet), undertaking regular exercise, smoking cessation and adhering to moderate alcohol consumption (a limit of two drinks per day in most men, and no more than one drink per day in women and lighter-weight individuals). These lifestyle modifications are effective interventions that decrease BP, reduce cardiovascular risk and enhance the efficacy of drug treatments.[4] One of the easiest dietary modifications is the reduction of sodium intake to <100 mmol/day, which has been shown to substantially reduce BP in patients with hypertension, especially when combined with the DASH diet.[12]

Table I. Key features of the optimal antihypertensive agent

Lowers blood pressure effectively
High efficacy as a monotherapy
Relatively rapid onset of antihypertensive efficacy
Convenient once-daily administration
Sustained efficacy over 24 hours
Response increases with higher dosages
Excellent tolerability profile
Ability to reduce the incidence of negative or poor cardiovascular outcomes

Normal BP has been defined as a systolic BP (SBP) of <120mm Hg and a diastolic BP (DBP) of <80mm Hg (table II).[4] In the JNC 7 report, the new category of 'prehypertension' was introduced and defined as a SBP of 120–139mm Hg or a DBP of 80–89mm Hg.[4] Those individuals with prehypertension do not require pharmacological therapy, but should adopt lifestyle modifications to lower their BP and cardiovascular risk (table II).[4] Drug treatment is recommended for patients with BP that falls into stage 1 hypertension (defined as SBP 140–159mm Hg or DBP 90–99mm Hg) or higher. Notably, European guidelines have not adopted the prehypertension term as a specific BP category and have, instead, opted to retain the term 'high normal'.[9] An assessment of high total risk in this category would necessitate antihypertensive drug treatment, while moderate risk would indicate lifestyle changes.

Although many BP-lowering agents can be used as initial antihypertensive therapy, JNC 7 recommends starting with a thiazide diuretic for most patients, either alone or in combination with an agent from another class. When patients have compelling indications (table III),[4] treatment needs to be tailored to their individual conditions. Rather than specifically recommending first-line use of thiazide diuretics, European guidelines recommend

Table II. JNC 7 guidelines for the classification and management of blood pressure (BP) in adults[4]

BP classification	SBP[a] (mm Hg)		DBP[a] (mm Hg)	Management		
				lifestyle modification	initial drug therapy	
					without compelling indication	with compelling indication[b]
Normal	<120	and	<80	Encourage		
Prehypertension	120–139	or	80–89	Yes	No antihypertensive drug indicated	Drug(s) for the compelling indications[c]
Stage 1 hypertension	140–159	or	90–99	Yes	Thiazide-type diuretic for most; may consider ACE inhibitor, ARB, β-blocker, CCB or combination	Drug(s) for the compelling indications Other antihypertensive drugs (diuretic, ACE inhibitor, ARB, β-blocker, CCB) as needed
Stage 2 hypertension	≥160	or	≥100	Yes	2-drug combination for most (usually thiazide-type diuretic and ACE inhibitor, ARB, β-blocker, CCB)[d]	Drug(s) for the compelling indications Other antihypertensive drugs (diuretic, ACE inhibitor, ARB, β-blocker, CCB) as needed

a Treatment determined by highest BP category.

b See table III.

c Treat patients with diabetes mellitus or chronic kidney disease to a goal BP of <130/80mm Hg.

d Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

ACE = angiotensin-converting enzyme; **ARB** = angiotensin receptor blocker; **CCB** = calcium channel antagonist or blocker; **DBP** = diastolic BP; **JNC 7** = Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; **SBP** = systolic BP.

all major classes of antihypertensive agents, including diuretics, calcium channel antagonists, ACE inhibitors, angiotensin receptor antagonists or blockers (ARBs) and β-adrenoceptor receptor blockers (β-blockers), as potential choices for individualised first-line treatment.[9] However, on the basis of analyses indicating suboptimal results with β-blockers,[13,14] it has since been suggested that guideline committees will need to reassess endorsement of β-blockers as reasonable first-line drugs for the primary prevention of cardiovascular events in patients with hypertension.[15]

The reality of patient care is that many patients present for treatment with a BP that is categorised as stage 2 hypertension (defined as SBP ≥160mm Hg or DBP ≥100mm Hg) and will require more than one drug to reach a normotensive level. This has been repeatedly demonstrated in large-scale clinical trials, including the HOT (Hypertension Optimal Treatment) trial, the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study and ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial).[16-18] The optimal management plan for patients such as this would be to select drugs from different classes with complementary mechanisms of action[4] because greater BP reductions are required for these patients to reach goal BP. This strategy allows the clinician to use lower doses of multiple medications rather than to attempt to manage patients with higher doses of a single drug. Therapeutic options include either single agents or fixed-dose combinations.

In many cases, patients with co-morbid conditions respond better to medications in particular drug classes. For example, patients with diabetes should be managed with ACE inhibitors or ARBs because of the renoprotective effects and the ability of these medications to reduce and maintain goal BP. Patients of African American descent may have a more favourable response to diuretics or calcium channel antagonists but, in some cases, a less favourable response to β-blockers or ACE inhibitors. ACE inhibitors can occasionally lead to the development of angioedema (0.1–0.7% incidence) but, for reasons not clearly understood, the incidence of angioedema is at least three times higher in African American patients treated with ACE inhibitors.[19-22] The adverse-effect profiles of all medications

should be reviewed carefully by clinicians before any medication is prescribed, and these will require especially close monitoring in certain groups of patients. For example, in elderly patients, electrolyte imbalances and orthostatic hypotension often occur with diuretics and vasodilators, respectively. Although these medications provide the desired BP-lowering effect, elderly patients must be monitored closely if these medications are selected for BP management.

2. Lowering Blood Pressure to Recommended Goals

The relationship between BP and cardiovascular disease risk is continuous and independent of other risk factors.[4] For individuals between 40 and 70 years of age with an initial BP of 115/75mm Hg, the risk of cardiovascular disease doubles with each 20/10mm Hg increment in BP.[2] Treating BP to the recommended goals of <140/90mm Hg and <130/80mm Hg in patients with diabetes or chronic kidney disease, respectively, is associated with a decrease in cardiovascular disease complications.[4]

For many years, clinicians have subscribed to the belief that reducing DBP confers a greater benefit to patients than reducing SBP. Whereas reducing SBP to target levels is often more difficult than is reducing DBP, it is associated with greater cardiovascular risk reduction than is lowering DBP in patients >50 years of age.[23-25] Many clinicians unwittingly allow patients to maintain a BP that is 'close to goal' and become complacent and satisfied with this clinical achievement. Despite evidence that demonstrates improved cardiovascular risk status when BP is controlled to goal, less than 30% of non-diabetic and 11% of diabetic patients are considered to have BP controlled to goal.[26]

Clinicians and patients alike should not accept treated BP values that just get 'close to goal'. Cardiovascular risk reduction can be achieved only when the patient's primary care provider has an organised patient monitoring system that documents BP measurements, prompts the regular recall of patients with hypertension, facilitates the tracking of BP goals, and encourages adherence to treatment through the use of algorithms.[27] The value of guidelines and algorithms that encourage drug dosage titration (in which drug dosages are increased and/or additional antihypertensive agents added) in reaching and maintaining BP goals has been demonstrated in a number of clinical trials.

In the HDFP (Hypertension Detection and Follow-up Program),[28] patients with a baseline DBP >90mm Hg were randomised to regular-care or stepped-care. In the regular-care arm, patients received the usual care customarily followed by their provider. In the stepped-care group, patients were encouraged to attend clinics and were monitored more rigorously through assessment of pill counts, and treatment was increased until BP goals were reached. After 5 years, the group managed more aggressively had lower mean BP values, greater achievement of goal BP, and lower rates of all-cause mortality compared with the regular-care group.[28]

Table III. JNC 7 guidelines for the choice of therapy in patients with compelling indications[4]

High-risk conditions with compelling[a] indication	Recommended drugs					
	diuretic	β-blocker	ACE inhibitor	ARB	CCB	aldosterone antagonist
Heart failure	✓	✓	✓	✓		✓
Post-myocardial infarction		✓	✓			✓
High coronary disease risk	✓	✓	✓		✓	
Diabetes	✓	✓	✓		✓	
Chronic kidney disease			✓	✓		
Recurrent stroke prevention	✓		✓			

a Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.

ARB = angiotensin receptor blocker; **CCB** = calcium channel antagonist or blocker; **JNC 7** = Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

In the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) study,[29] patients with hypertension were randomised to receive either valsartan or amlodipine. If the patients did not reach the BP goal of <140/90mm Hg on initial therapy, additional steps were taken at monthly intervals to lower BP. Firstly, the dosage could be increased, then hydrochlorothiazide added and finally additional antihypertensives were added. At baseline, 92% of patients were receiving antihypertensive agents but only 21.9% had a SBP <140mm Hg. Using this model, SBP control increased to 59.5% after 24 months of treatment and 62.2% after 30 months.

In a meta-analysis of randomised clinical trials of BP lowering, no single class of agent was significantly more effective than another in terms of reducing the risk of cardiovascular events.[30] This analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration[30] also showed that intensive regimens that lowered DBP to <85mm Hg were significantly more effective in reducing stroke (by 20%), coronary heart disease (by 19%) and major cardiovascular events (by 15%) than were regimens with less intensive BP goals. However, it should be noted that this analysis did not include ARBs because no major randomised trials had been published in the time frame of the meta-analysis. A subsequent meta-analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration, which did include trials involving ARBs, concluded that antihypertensive regimens based on any commonly used class of agent reduces the risk of major cardiovascular events.[31] Again, it was emphasised that the largest reductions occur with intensive regimens targeting lower BP goals.[31] The results of a number of other meta-analyses performed after randomised trials with ARBs began to be published, also confirm the importance of tight BP control and caution that, in the majority of hypertensive patients, more than one class of antihypertensive drug is required to achieve this, including use of a low-dose thiazide-type diuretic at the first treatment step.[32-34]

3. High Efficacy as a Monotherapy in Terms of Treatment to Goal

Antihypertensive therapy is most likely to be successful when BP goals and treatment algorithms are defined.[4,35] Clinical evidence suggests that most patients will require more than one drug to reduce BP to goal.[16-18,29,36] So, in the majority of patients, effective monotherapy still remains an elusive goal. However, monotherapy alone may be successful in some patients, particularly those with JNC 7 criteria for stage 1 hypertension. JNC 7 guidelines recommend that most patients with uncomplicated stage 1 hypertension initiate treatment with a thiazide-type diuretic or, if certain compelling indications are present, an ACE inhibitor, ARB, β-blocker or calcium channel antagonist may be used (table II).[4] A second drug should be added early in the course of therapy for those patients with BP not controlled with monotherapy. Initially treating patients with stage 2 hypertension may help more patients achieve goal BP faster with combination therapy.

Historically, most studies evaluating the efficacy of antihypertensive agents have concentrated on mean reductions in BP achieved by a drug, rather than final absolute BP values. However, several clinical trials have employed treatment algorithms based on different pharmacological agents in order to reduce BP to a predetermined goal.[16-18,29,36] Relatively high BP control rates were achieved in these trials, but goal SBP was more difficult to reach than DBP (success rates of approximately 50–60% with SBP vs 90% with DBP), and over two-thirds of patients required treatment with two or more antihypertensive drug classes.

Starting treatment with a renin-angiotensin system inhibitor is now a common first step in the treatment of hypertension, and reports of the efficacy of ARBs in reducing both SBP and DBP to goal are emerging in the literature. In a recent review, Oparil and colleagues reported that monotherapy with an ARB is capable of achieving both SBP and DBP goals (<140/90mm Hg) in 15% to 32% of hypertensive patients (figure 1).[37,38] The study under review examined secondary data from a previ-

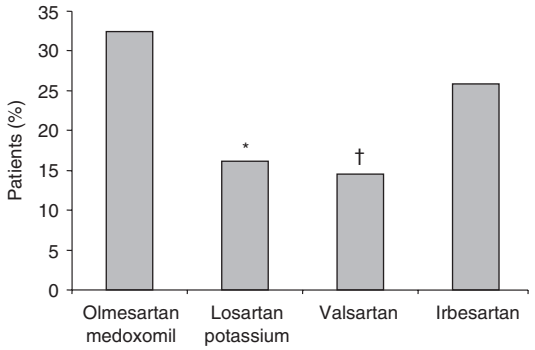

Fig. 1. Proportion of patients achieving the recommended goal blood pressure <140/90mm Hg after 8 weeks of once-daily therapy with starting doses of olmesartan medoxomil 20mg, losartan 50mg, valsartan 80mg or irbesartan 150mg once daily. * $p < 0.01$ vs olmesartan medoxomil; † $p < 0.001$ vs olmesartan medoxomil (reproduced from Oparil et al.,[37] © 2005, with permission from the American Journal of Hypertension, Ltd).

ously reported study on optimal ARB starting dosages and captured 24-hour ambulatory BP readings in almost 600 patients.[38] Most recently, a subanalysis of results from an open-label study of an ARB-based structured treatment algorithm in 79 patients with stage 1 hypertension and 100 patients with stage 2 hypertension by Neutel and colleagues[39] reported achievement of goal BP with monotherapy in 80% and 42% of patients, respectively. The remainder of patients with stage 1 hypertension generally attained goal BP with ARB plus thiazide diuretic two-drug therapy (94% cumulative rate of success). There was little additional benefit of adding a third drug in this patient population. In patients with stage 2 hypertension, the cumulative rate of treatment success was 75% for two-drug therapy and 90% with addition of a calcium channel antagonist (triple therapy). Stepped-care approaches, such as that described by Neutel and colleagues,[39] recognise the importance of reducing both SBP and DBP values to goal and achieving this with the least amount of medication.

Achieving goal BP with monotherapy has a number of advantages. Firstly, using fewer agents has the potential to minimise the cost of therapy.[40] Secondly, a less complicated regimen may be associated with better patient compliance and persistency.[41,42] Thirdly, the use of more than one antihypertensive agent tends to increase the proportion of patients reporting adverse effects with medication.[43]

When patients are prescribed more than one antihypertensive medication, patient adherence can be compromised on the basis of tolerability and compliance. Different classes of antihypertensive agents have different class-specific adverse events (table IV), and the use of more than one agent can potentially result in increased adverse effects and drug-drug interactions. In the study by Neutel and colleagues,[39] however, the overall incidence of treatment-emergent adverse events was no greater in patients with stage 1 or stage 2 hypertension treated with double therapy or triple therapy than in patients who only required monotherapy (no more than about 40%). This observation shows that it is possible to use multiple drugs to attain BP goals in patients with stage 2 hypertension without increasing the burden of adverse events. However, unless the combination is available in a fixed formulation, the patient must remember to take additional medications. Fixed combinations can simplify drug regimens and improve compliance (relative to taking multiple separate drugs). They can also mitigate any clinical reluctance to treat hypertension aggressively. However, if a patient's initial therapy is a fixed combination and he or she reports drug-related adverse effects, the clinician must promptly attempt to differentiate which agent is the cause and modify the regimen if the adverse effect is of sufficient consequence to warrant a change in medication.

4. Rapid Onset of Antihypertensive Efficacy

European and US treatment guidelines encourage aggressive initiation of antihypertensive therapy to prevent cardiovascular morbidity and mortality.[4,9,56] A *post hoc* analysis of the VALUE trial concluded that rapid reduction of BP, independent of the type of drug used, is the primary predictor of event rates.[57] Patients were categorised as 'immediate' BP responders if they had no increase in BP by 1 month after switching from previous therapy or an initial decrease in systolic BP of ≥10mm Hg at 1

Table IV. Typical adverse effects with commonly used antihypertensive agents[44-46]

Drugs	Adverse effect
Diuretics[47,48] (e.g. HCTZ, chlorthalidone)	Hypokalaemia Hypomagnesaemia Hypercalcaemia Increased levels of serum cholesterol (long-term high-dose use) Hyperglycaemia Hyperuricaemia or gout Impotence
β-Blockers[49] (e.g. atenolol, metoprolol, propranolol, nebivolol)	Bradycardia Insomnia Depression Nightmares Elevated serum triglycerides (less tendency with β_1-selective agents) Impaired glucose control and reduced awareness of hypoglycaemia (less tendency with β_1-selective agents) Fatigue or asthenia Reduced exercise performance Impotence
α-Blockers[50] (e.g. doxazosin, prazosin)	Headache Postural hypotension Dizziness Drowsiness Fatigue Urinary incontinence (women) Tachycardia
Combined α- and β-blockers[51] (e.g. labetalol, carvedilol)	Adverse events associated with pure α-blockers or pure β-blockers (see above) Orthostatic hypotension Hepatotoxicity (labetalol)
Central sympatholytics[52] (e.g. clonidine, methyldopa, moxonidine, rilmenidine)	Sedation Dry mouth Sexual dysfunction
Calcium channel antagonists[53] (e.g. amlodipine, felodipine, nifedipine)	Headache (dihydropyridines) Flushing (dihydropyridines) Tachycardia (dihydropyridines) Peripheral oedema (dihydropyridines) Gingival hyperplasia (dihydropyridines) Constipation (verapamil) Atrioventricular block (verapamil)
ACE inhibitors[54] (e.g. captopril, enalapril, lisinopril, perindopril, ramipril)	Cough Angioneurotic oedema Renal dysfunction (in patients with renal disease) Skin reactions (sulfhydryl-containing agents [e.g. captopril]) Taste disturbances (sulfhydryl-containing agents [e.g. captopril]) Hypokalaemia Hypotension
ARBs[55] (e.g. candesartan cilexetil, losartan, olmesartan medoxomil, telmisartan, valsartan)	Hypokalaemia Renal impairment Hypotension Oedema

ARB = angiotensin receptor blocker; **HCTZ** = hydrochlorothiazide.

month if they were not previously treated. These patients had a significantly reduced risk of cardiac events, stroke and death (figure 2) compared with 'nonimmediate' BP responders.[58]

To assess the impact of early versus delayed treatment in elderly patients with isolated systolic hypertension, the randomised, double-blind SYS-EUR (Systolic Hypertension in Europe) trial was

extended by a 4-year open-label follow-up.[59] Almost 4700 patients were included in the follow-up group. Those demonstrating early response to antihypertensive therapy had 28% fewer strokes ($p = 0.01$) and cardiovascular sequelae ($p = 0.03$). These findings are similar to those seen in the VALUE trial. The benefits of early treatment were even more evident in patients with co-morbid diabetes, who showed reductions in stroke, cardiovascular complications and mortality of 60%, 51% and 38%, respectively (all $p < 0.02$). As a result of these findings, the study investigators proposed that immediate treatment with antihypertensives could prevent 17 strokes or 25 major cardiovascular events per 1000 patients over 6 years.

Few studies have compared various agents' ability to achieve early BP reduction; however, those that have demonstrated some promising results. In the VALUE trial, amlodipine was found to have a rapid onset of antihypertensive effect, compared with valsartan.[57] Data from this trial indicated that amlodipine achieved greater mean BP reductions within the first month of treatment and was associated with a significantly lower rate of myocardial infarction ($p = 0.02$). In an attempt to overcome inequalities in BP, serial median matching at 6 months was used to create 5006 valsartan-amlodipine patient pairs matched for SBP (mean 139.9mm Hg) and other variables. In this analysis, most outcomes, including the primary composite endpoint of cardiac morbidity and mortality, were similar for the two regimens.[58]

When the VALUE study was designed, the usual clinical dose range for valsartan was 80–160 mg/day. It has subsequently been shown that higher doses are required for full angiotensin II blockade[60] and a 160–320 mg/day dose range has now been approved. It has also been recommended that, instead of treatment initiation involving immediate roll-over to a low dose of study drug, as occurred with valsartan in VALUE, more stringent initial control of BP should be an ethical requirement for clinical trials involving patients with hypertension.[58] For example, it is important to titrate ARBs adequately and rapidly, and the addition of a low-dose thiazide diuretic at the first treatment step should be considered in high-risk hypertensive patients. Clinicians need to integrate rapidity of pharmacological action into their therapeutic decision making, especially in patients at high risk for cerebrovascular and cardiovascular events.

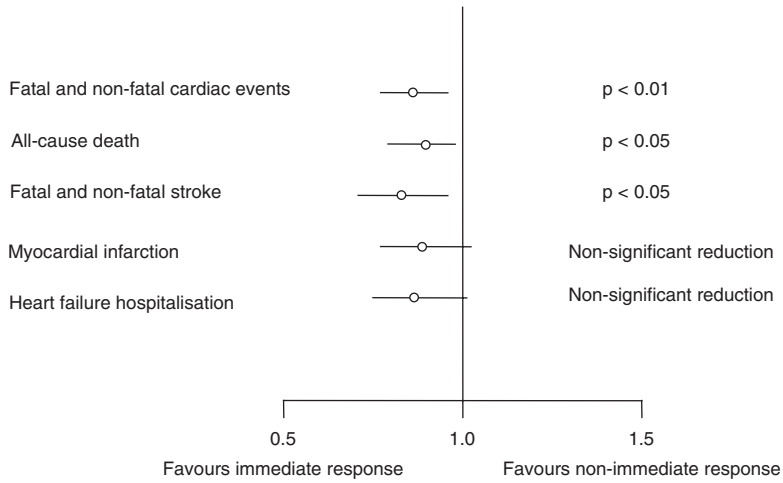

Fig. 2. Hazard ratios with 95% confidence intervals for subsequent events in immediate blood pressure (BP) responders (those who had no increase in BP within 1 month when switched from their current medication to the study drug or who had a decrease in systolic BP of ≥10mm Hg if not previously treated) and non-immediate responders in the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial.[58] An early BP-lowering response was associated with a significant reduction in cardiovascular outcomes.

5. Convenient Once-Daily Administration

One of the most difficult realities that patients with hypertension must accept is that hypertension is generally lifelong and requires daily pharmacological therapy. To enhance patient adherence to therapy, the convenience of once-daily administration is a definite advantage.[61]

A number of studies show that simplifying dose administration regimens can improve adherence in patients with hypertension.[42] A recent review of 30 hypertension trials showed that mean compliance for a once-daily antihypertensive regimen was 94.0% compared with 88.2% for a twice-daily regimen.[62] In addition to improving compliance, simplifying the regimen from twice to once daily has been shown to reduce SBP by about 6mm Hg.[63]

There is also strong evidence to indicate that drug class is a significant predictor of patient compliance.[64] An analysis of data from 46 458 Canadian patients with hypertension showed that patients taking ARBs were the most compliant, followed by patients taking ACE inhibitors, calcium channel antagonists, β-blockers and diuretics.[64] Even within drug classes, there are differences that affect the ability of a drug to control BP with once-daily administration. For example, whether an ARB competitively or noncompetitively binds with angiotensin II type 1 receptors can affect the duration of action. All of these factors must be evaluated when designing a therapeutic plan for a patient's hypertension treatment.

6. Maintenance of Efficacy Throughout the 24-Hour Administration Period

The incidence of cardiovascular events often follows a circadian pattern, with the majority of events occurring in the morning after waking and rising from bed. This heightened cardiovascular risk may in part be explained by circadian variations in BP.[65-67] BP is known to fall during sleep and rise sharply on awakening and standing (figure 3). This 'morning surge' in BP may trigger various cardiovascular events, including myocardial infarction and stroke.[68]

Given these findings, it is important that antihypertensive therapy provides BP control throughout the administration period. Since many antihypertensive agents are administered in the morning, the time of trough plasma concentrations will often coincide with the early morning surge in BP. Consequently, use of long-acting antihypertensive agents that provide 24-hour BP-lowering coverage from a single daily dose, including attenuation of the early morning surge in BP, is the most desirable treatment option.

7. Demonstration of a Good Dose Response

The optimal dosage of an antihypertensive agent is the lowest maximally effective dosage. This allows patients to achieve the largest possible reduction in BP and avoid unnecessary adverse effects. As it is often necessary to increase the dose of a drug to achieve the required therapeutic effect, a higher dose of the drug should be associated with a beneficial increase in the clinical response. Increasing the dose of antihypertensive medication will result in an incremental decrease in BP. When titrating to higher dosages, it is important to evaluate the efficacy of BP reduction at these higher dosages. This strategy may enable a patient to reach goal BP on monotherapy, if the higher dosage produces the necessary BP-lowering efficacy.

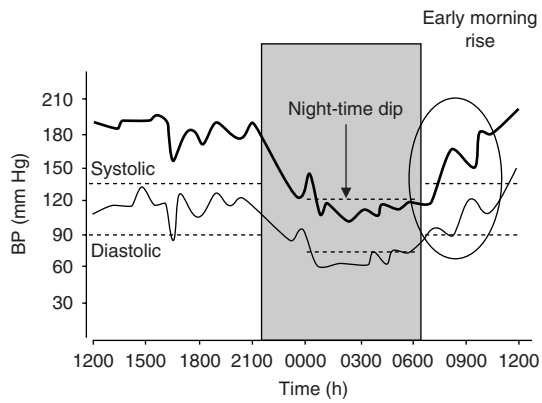

Fig. 3. Circadian variation in blood pressure (BP) over a 24-hour period in a patient with untreated hypertension. The shaded area is the night-time period and the dotted lines represent the normal limits for ambulatory BP.

8. Tolerability

It is critical that antihypertensive agents be well tolerated to ensure patient adherence. A European survey of randomly selected hypertensive patients showed that almost 20% of patients experience adverse effects with BP-lowering medication and that some of these effects – such as insomnia, sexual dysfunction, fatigue and depression – can significantly impair patient quality of life.[43] Studies have shown that adverse effects with treatment are one of the key reasons that patients taking antihypertensive agents switch to an alternative treatment.[44] Ideally, an antihypertensive agent would have a tolerability profile similar to that of placebo, with no significant increase in adverse events.

In general, most classes of antihypertensive agents are well tolerated, with newer agents having improved tolerability profiles compared with those of older agents. The ARBs have a tolerability profile similar to that of placebo in clinical trials.[45,69] The ACE inhibitors are generally well tolerated, although cough and angioneurotic oedema, thought to be associated with the accumulation of various substrates of angiotensin converting enzyme, may affect some patients.[19] In clinical trials, the agents most likely to be discontinued because of adverse events are calcium channel antagonists and α-blockers, and the agents least likely to be discontinued are ARBs and diuretics.[69] Common adverse-effect profiles of antihypertensive agents are shown in table IV.[44-46]

9. Proven Ability to Reduce the Incidence of Cardiovascular Outcomes

One of the primary goals of antihypertensive therapy is to reduce the incidence of negative or poor cardiovascular events in patients with hypertension. To this end, the encouraging news is that all classes of antihypertensive drugs have been shown to reduce the incidence of cardiovascular events. In general, antihypertensive therapy has been shown to reduce the incidence of heart failure by >50%, myocardial infarction by 20–25% and stroke by 35–40%.[30] Historically, thiazide-type diuretics have been the cornerstone of antihypertensive therapy and have been shown to reduce cardiovascular disease events, including coronary heart disease, heart failure and strokes.[4] However, numerous clinical trial data published over the last 20 years show that all classes of antihypertensive agents, including β-blockers, calcium channel antagonists, ACE inhibitors and ARBs, have beneficial effects in reducing cardiovascular events.[4]

A meta-analysis by Psaty et al.[34] comparing long-term randomised controlled trials that assessed major cardiovascular disease endpoints revealed that non-diuretics reduced cardiovascular outcomes to a similar extent as seen with diuretics. However, diuretics did show a significantly greater reduction in risk for congestive heart failure, stroke and cardiovascular disease events versus ACE inhibitors, cardiovascular disease events versus β-blockers, and congestive heart failure versus calcium channel antagonists. Additional differences have been shown between some classes of agents regarding specific outcomes. In the ALLHAT, a calcium channel antagonist or an ACE inhibitor showed a significantly greater reduction in risk for heart failure than a diuretic. Similarly, the ACE inhibitor was better than the diuretic for reducing the risk of stroke.[70] LIFE demonstrated that an ARB-based regimen was better than a β-blocker-based regimen for stroke reduction and preventing cardiovascular morbidity and mortality.[16] One explanation for these observed differences in specific outcomes is that some classes of antihypertensive agents have inherent organ-protective effects independent of their BP-lowering abilities. For example, in the LIFE trial, both the ARB and the β-blocker reduced BP to a similar extent and yet the ARB was significantly better at reducing the endpoints mentioned above, as well as the rate of new-onset diabetes compared with the β-blocker.[16] These differences between drug therapies are reflected in the JNC 7 recommendation that when certain compelling indications are present, then specific classes of agents should be used as initial therapies (table III).

10. Conclusions

Although advances in the treatment of hypertension have been made over the last 20 years, hypertension remains a leading cause of cardiovascular morbidity and mortality. More than two-thirds of patients with hypertension fail to achieve recommended BP goals in the US.[5] Physicians and other clinical providers have an important role to play in improving BP control rates through patient education, regular follow-up, monitoring for adverse events and encouraging adherence to therapy.

The lack of aggressive monitoring and reluctance to increase dosages or add a second drug is now believed to be a significant factor that contributes to poor BP control rates in the US.[6,8,44] A number of studies have shown that, even when a patient's BP is above goal, physicians are more likely to monitor BP than to change treatment; an increase or change in antihypertensive treatment is instituted in less than 25% of cases.[6,7] Providers are inclined to accept higher BP values in older patients and those with obesity[25,71] or left ventricular hypertrophy.[25]

Ideally, clinicians should choose an initial antihypertensive agent that will provide the patient with the best opportunity of achieving his or her BP goal. The optimal antihypertensive agent should be one that lowers BP to goal, demonstrates a quick onset of effect, is well tolerated, has high efficacy as a monotherapy, has a convenient dose administration schedule, maintains efficacy throughout the 24-hour dose administration period, has a clear dose-response relationship, and reduces the incidence of cardiovascular outcomes.

Currently, no single antihypertensive agent or class of antihypertensive agents can be considered 'optimal', although recent advances in therapy have brought improvements that are moving us closer to the 'ideal'. Many agents are now available in once-daily formulations to maximise compliance, have tolerability profiles similar to that of placebo and provide antihypertensive coverage through the early morning hours. Nevertheless, treatment needs to be tailored to individual patients, taking into account their concomitant conditions, family history, ethnicity, age and socioeconomic situation. The most important thing to recognise is that hypertension, although often asymptomatic, is far from benign, and long-term treatment (either with monotherapy or combination therapy) to recommended goals is the best way to reduce long-term cardiovascular risk associated with poorly controlled hypertension.

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