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REVIEW

Optimizing hypertension management in clinical practice

A Heagerty
Cardiovascular Research Group, Division of Cardiovascular and Endocrine Sciences, Core Technology Facility (3rd Floor), University of Manchester, Manchester, UK

A clear relationship exists between elevated blood pressure (BP) and various manifestations of cardiovascular disease. Despite the availability of numerous treatment guidelines, hypertension remains inadequately controlled, with only a small proportion of patients achieving target BP levels. Many factors, both patient and physician related, contribute to this poor level of hypertension control. Major determinants include the implementation of inappropriate treatment regimens that do not enable patients to achieve goal and poor patient compliance. For example, it is widely acknowledged that most patients require two or more antihypertensive drugs to achieve BP goal; however, physicians may be reluctant to employ such treatment strategies. The aim of this review is to explore factors that contribute to poor hypertension control rates and how to overcome these, including the rationale for selecting combination therapy, with particular reference to angiotensin II receptor blocker combinations.
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Introduction

According to the World Health Organization, hypertension is the most prevalent risk factor for cardiovascular (CV) disease. It affects approximately 20% of the adult population and has been estimated to be responsible for at least 7 million deaths each year.[1] Furthermore, it is projected that by 2025, 29% (over 1.5 billion adults) of the world's population will have hypertension.[2] Much of the associated morbidity and mortality is potentially avoidable, providing that patients with hypertension are identified and treated appropriately. There is now a wealth of evidence from clinical trials to suggest that effective blood pressure (BP) control is achievable in the majority of patients and can significantly reduce the impact of hypertension in terms of general health, disability and early mortality.[3,4] For example, intensive antihypertensive drug treatment for patients with uncomplicated hypertension has been shown to reduce the incidence of stroke, myocardial infarction (MI) or heart failure by 35–40, 20–25 and $>50\%$, respectively.[5] Additionally, in patients with other CV risk factors (Table 1) and systolic BP (SBP) of 140–159 mm Hg and/or diastolic BP (DBP) of 90–99 mm Hg (stage 1 hypertension), it has been estimated that a 10-year, sustained reduction of 12 mm Hg in SBP will prevent one death for every 11 patients treated, and that if CV disease or end-organ damage is already present, this ratio improves to one life saved for every nine patients treated.[8]

Despite encouraging clinical data, current real-life medical practice does not appear to deliver the health benefits that should be possible from BP reduction. For the most part this may reflect that BP control rates (i.e. patients achieving BP goal) remain unacceptably low in many patient groups.[9–14] As a matter of urgency, it is necessary to explore the underlying reasons for inadequate BP control and implement effective treatment to address these issues.

The aim of this review is to discuss the ways in which both patient and physician-related factors contribute to the lack of BP control and how these issues can be addressed in order to realize the benefits of antihypertensive therapy in clinical practice.

A non-systematic literature search using Medline database was performed to support, validate and strengthen the clinically derived observations and experience presented here. This review included evaluation of epidemiological studies, clinical trials, outcomes studies and surveys. All recommendations presented here are supported by clinical evidence in the literature.

Correspondence: Professor A Heagerty, Cardiovascular Research Group, Division of Cardiovascular and Endocrine Sciences, Core Technology Facility (3rd Floor), University of Manchester, 46 Grafton Street, Manchester M13 9NT, UK.
E-mail: tony.heagerty@manchester.ac.uk
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Table 1 Risk factors for CV disease identified in the JNC-7 guidelines (from Chobanian *et al.*, 2003[6,7])

Major CV risk factors
Hypertension
Cigarette smoking
Obesity (BMI $\geqslant 30\,kg/m^2$)
Physical inactivity
Dyslipidaemia
Diabetes mellitus
Microalbuminuria or estimated GFR <60 ml/min
Age (>55 years for men, >65 years for women)
Family history of premature CV disease (men <55 years or women <65 years)
Target organ damage
Heart
Left ventricular hypertrophy
Angina or myocardial infarction
Prior coronary revascularization
Heart failure
Brain
Stroke or transient ischaemic attack
Chronic kidney disease
Peripheral arterial disease
Retinopathy

Abbreviations: BMI, body mass index; CV, cardiovascular.

Addressing the problem

A number of approaches to improving BP control are possible in routine practice. Increasing physicians' awareness of current treatment guidelines and recommended target BP is necessary to promote optimal management strategies. Realizing the benefits of antihypertensive therapy observed in clinical trials can also be facilitated by helping physicians to make appropriate treatment choices and utilize optimal doses for individual patients based on their CV risk profiles. Also, there is evidence that patient compliance (taking medication as indicated) with prescribed antihypertensive medication is poor and lifestyle advice is inadequate.[15] Consequently, initiatives to improve patients' understanding of their condition, leading to improved compliance,[15] may contribute to better BP control. Other approaches to improving BP control in clinical practice include close monitoring of patients to identify secondary causes of hypertension that require alternative management, or ingestion of substances that can affect BP and/or interact with prescribed antihypertensive medication.

Treatment guideline recommendations

Numerous national and international guidelines exist for the management of hypertension. Currently, the most influential guidelines in North America and Europe are the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7),[6] and the Guidelines of the European Society of Hypertension and European Society of Cardiology, respectively.[16] Both sets of guidelines are based upon evidence from well-conducted clinical research and are intended to provide physicians with a rational and practical approach to prevention, diagnosis and management.

The guidelines highlight the importance of the diagnostic assessment and emphasize the need to identify any treatable causes of hypertension as well as additional risk factors for CV disease (Table 1). Without a patient's full disease and CV risk profile, appropriate treatment goals and management programmes cannot be determined, as guidelines recommend that different target BP goals should be set, and different antihypertensive drugs prescribed, depending on the patient's CV risk profile.[17,18] As outlined by the JNC-7 and European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines, the target BP goal for most patients with uncomplicated hypertension is $<140/90$ mm Hg. However, the more stringent goal of $<130/80$ mm Hg is indicated for patients with diabetes mellitus or renal disease.[6]

Although the majority of physicians support the concept of guidelines, several surveys suggest that recommendations are not employed in the vast majority of cases,[19–25] contributing to suboptimal BP control and increased morbidity and mortality. The effects of this cannot be overstated; it has been estimated that if all guideline recommendations were implemented, the number of clinical coronary events could be reduced by as much as one-third.[26] Therefore, it is imperative for physicians to familiarize themselves with current guideline targets and implement the most appropriate treatment regimens to enable patients' to achieve their BP goal and maximize treatment benefit.

Lifestyle modifications

Guidelines emphasize that lifestyle modifications, which include exercise, a healthy diet, reduced salt intake and stress management, are the cornerstone of the management of patients with hypertension (Table 2). However, poor compliance with lifestyle changes has been reported to be an important contributing factor to inadequate BP control.[27] Compliance is intrinsically linked with physician guidance; however, studies indicate that the importance of lifestyle modifications may be inadequately emphasized sometimes by health-care professionals.[28] Physician guidance may be restricted by insufficient time for counselling and limited training on effective techniques, low reimbursement rates for counselling and physician pessimism about the willingness of patients to change negative health habits.[28] However, it is essential for physicians to emphasize the merits of lifestyle modifications, and the associated positive impact they have on BP, if adhered to as part of an overall treatment strategy to improve BP control.

Table 2 Lifestyle modifications to prevent and manage hypertension[7]

Modification	*Recommendation*	*Approximate SBP reduction (range)*
Weight reduction	Achieve and maintain normal body weight (BMI: 18.5–24.9 kg/m^2). For example: ● Decrease portion sizes for meals, snacks ● Reduce portion sizes or frequency of consumption of high-calorie beverages ● Reduce energy intake by 500 kcal/day	5–20 mm Hg/10 kg
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Dietary sodium reduction	Reduce dietary sodium intake to $\leqslant$100 mmol/day (2.4 g sodium or 6 g sodium chloride). NB: a high sodium intake is especially deleterious in overweight individuals	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activities that raise the heart rate, such as brisk walking ($\geqslant$30 min/day, most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to $\leqslant$2 drinks per day in most men and to $\leqslant$1 drink per day in women and lighter-weight persons	2–4 mm Hg

Abbreviations: BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; SBP, systolic blood pressure.[7]

Education often prompts patients to be more involved in managing their condition, thereby increasing compliance. In order to implement lifestyle changes effectively, an interdisciplinary approach may be required, and referral to a dietitian or nutritionist may be warranted.

Pharmacological treatment

In addition to lifestyle modifications, the majority of patients require pharmacological intervention to achieve BP goal.[7] The JNC-7 guidelines recommend that thiazide-type diuretics should be used as initial therapy for most patients with uncomplicated hypertension either alone or in combination with one other class of agent (β-blockers (BBs), calcium-channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)).[7] A number of indications require the use of other antihypertensive drugs as initial therapy, as outlined in Table 3. The primary goal of treatment must be to ensure that patients reach BP goal in a timely manner, as this largely determines clinical outcome. However, as the publication of the JNC-7[7] and ESH-ESC[29] guidelines in 2003, new data that question some of the existing antihypertensive drug recommendations outlined in these guidelines have emerged. For example, the use of BBs, the mainstay of therapy and often the first drug of choice, has been called into question.[30] This is primarily as a result of the poor performance of atenolol, one of the most widely used BBs, clinically as the initial drug in the ASCOT-BPLA trial (Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm).[31] The trial was halted prematurely owing to the superiority of ACE inhibitor/CCB treatment versus BB/diuretic therapy in terms of reductions in primary end point (non-fatal MI), fatal and non-fatal stroke, total CV events and procedures, and all-cause mortality, despite similar reductions in BP. The incidence of developing diabetes was also lower on the CCB-based regimen versus the BB-based regimen. Earlier support for limiting the use of BBs came from a meta-analysis showing that atenolol was not as favourable in clinical outcome as other therapies.[32] When atenolol was compared with other antihypertensives, no major differences in BP lowering between the treatment arms were observed. The meta-analysis showed a significantly higher overall mortality with atenolol treatment than with other active treatments. Moreover, CV mortality tended to be higher with atenolol treatment than with other antihypertensive treatments. Stroke was also more frequent with atenolol treatment and atenolol was found to be only slightly better than placebo in stroke reduction.[32] Furthermore, a recently performed meta-analysis of BBs as a group showed that the observed poor performance of atenolol in stroke reduction was not restricted to this agent but was a class effect.[33] The analysis reported that the risk of stroke was 16% higher for BBs than for other antihypertensive classes. Finally, studies have shown there is an increased risk of new cases of diabetes if BBs are combined with a diuretic, compared with the use of CCBs, ACE inhibitors or ARBs with or without a diuretic.[30] The outcomes of ASCOT, the aforementioned meta-analyses and other studies may have prompted the revision to the UK National Institute for Health and Clinical Excellence Clinical Guideline 18 that outlines recommendations for the management of hypertension in adults in primary care. The partial update indicates that BBs are no longer preferred as a routine initial therapy for hypertension. The update also specifies that the use of thiazide-type diuretic monotherapy as a first-line treatment option should be reserved for patients aged over 55 years and black patients, irrespective of age.

For many patients, especially those with additional CV risk factors beyond elevated BP, the most appropriate antihypertensive therapy regimen may involve agents that target the renin–angiotensin–aldosterone system (RAAS), such as ACE inhibitors

Table 3 Indications and contraindications for the major classes of antihypertensive drugs (from ESH/ESC guidelines[16] 2003)

Class	*Conditions favouring the use*	*Contraindications*	
		Compelling	*Possible*
Diuretics (thiazides)	Congestive heart failure Elderly hypertensives Isolated systolic hypertension Hypertensives of African origin	Gout	Pregnancy
Diuretics (loop)	Renal insufficiency Congestive heart failure		
Diuretics (anti-aldosterone)	Congestive heart failure Post-MI	Renal failure Hyperkalaemia	
β-Blockers	Angina pectoris Post-MI Congestive heart failure (up-titration) Pregnancy Tachyarrhythmias	Asthma COPD A-V block (grade 2 or 3)	Peripheral vascular disease Glucose intolerance Athletes and physically active patients
Calcium antagonists (dihydropyridines)	Elderly patients Isolated systolic hypertension Angina pectoris Peripheral vascular disease Carotid atherosclerosis Pregnancy		Tachyarrhythmias Congestive heart failure
Calcium antagonists (verapamil, diltiazem)	Angina pectoris Carotid atherosclerosis Supraventricular tachycardia	A–V block (grade 2 or 3)	
ACE inhibitors	Congestive heart failure LV dysfunction Post-MI Non-diabetic nephropathy Type I diabetic nephropathy Proteinuria	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	
ARBs	Type II diabetic nephropathy Diabetic microalbuminuria Proteinuria LV hypertrophy ACE inhibitor cough	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	
α-Blockers	Prostatic hyperplasia (BHP) Hyperlipidaemia	Orthostatic hypertension	Congestive heart failure

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MI, myocardial infarction.

and ARBs.[34] The CV benefits of blocking the RAAS have been demonstrated in large, long-term clinical trials involving many different patient populations including patients with MI, those at high risk for CV events and those with heart failure.[35] The evidence from several trials reveals that treatment with an ACE inhibitor or ARB, usually with a diuretic, reduces the frequency of CV events in patients at high risk more than regimens that do not include drugs that interfere with the RAAS.[36–41] Although efficacious, the limitations of treatment with ACE inhibitors should be noted, in particular, the tendency for treatment-related dry cough.[42] In contrast, ARBs provide more specific inhibition of the RAAS and this is thought to avoid the potential side effects noted with ACE inhibitors. Angiotensin II receptor blockers are selective antagonists for the angiotensin II type 1 receptor and have been shown to be efficacious and well-tolerated antihypertensive agents in many patient populations, including those in which BP control may be harder to achieve, such as elderly patients, black patients and obese patients.[43–45]

In addition to effective BP lowering, antihypertensive treatment regimens that include a RAAS blocking agent may confer additional cerebrovascular, CV and renal protection.[37–39,46–52] The findings of a recent study confirmed that blockade of the RAAS with ACE inhibitors afforded a 9% benefit in terms of protection against coronary heart disease in comparison with CCBs, despite comparable reductions in BP.[53] Therefore, it is possible to infer that long-term blockade of the RAAS with an ARB may afford the same benefit. Furthermore, reductions in new-onset diabetes with ARBs and ACE inhibitors relative to other antihypertensive medications have been noted in trials such as LIFE (Losartan Intervention For Endpoint reduction)[41] and VALUE (Valsartan Antihypertensive Long-term Use Evaluation).[54,55] Ongoing trials are expected to provide extensive comparative data between ARBs and other classes of antihypertensive agents and confirm that the benefits afforded by ARBs exceed that of BP lowering.[56]

Antihypertensive combination therapy

It is recognized that many patients will require two or more drugs to achieve BP goal (Figure 1). Initiation of combination therapy is recommended in patients whose BP is >20 mm Hg above the systolic goal or >10 mm Hg above the diastolic goal, either as separate agents or in a fixed-dose combination.[6] Although it can be argued that fixed-dose combination medications reduce the physician's ability to adjust doses of each component to suit individual patients' needs, their use can produce a better outcome. One key reason is that fixed-dose combinations simplify the regimen for patients, many of whom will be taking medications for other conditions, and increase compliance, as well as encouraging patients to persist with their medication.[58] It has also been argued that titration of dosage to achieve a particular BP target can be achieved more rapidly with fixed-dose combinations than with individual drugs, as the dosages of each of these are usually adjusted individually.[59] Furthermore, it may be more economical for a health-care system if patients are prescribed fixed-dose combinations rather than the same component drugs separately, owing to reductions in prescription costs and physician visits.[60]

Despite the proven effectiveness of an intensive approach to hypertension management in reducing morbidity and mortality, some physicians still appear reluctant to adopt an 'aggressive' approach whereby more than one agent is employed, which contributes significantly to inadequate control of hypertension.[61] This may be owing to general over cautiousness about the tolerability of antihypertensive agents.[61] However, ARBs typically have 'placebo-like' tolerability,[62] and when combined with hydrochlorothiazide (HCTZ), attenuate the disturbances in serum potassium, uric acid and blood glucose levels that are associated with higher doses of HCTZ.[63,64] Angiotensin receptor II blocker/HCTZ fixed-dose combinations not only have an additive effect on lowering BP (as with most antihypertensive combinations) but also have improved tolerability compared with other antihypertensive combinations.[63–71] Additionally, tolerability is retained irrespective of dose. In a recent study,[72] valsartan monotherapy (80 mg once daily) was effective in patients with stage 2 or 3 systolic hypertension. Significant additional reductions in SBP and DBP and an increase in responder rates were achieved with valsartan/HCTZ 160/12.5 and 160/25 mg and no significant effect on tolerability was observed.[72] Valsartan/HCTZ 320/12.5 and 320/25 mg once daily have also proven to be efficacious, well-tolerated treatment options.[73] The comparable efficacy[69] but improved tolerability of ARBs in comparison with other classes of antihypertensive agents[66,69] further supports the use of ARB combinations as first-line treatment for hypertension.

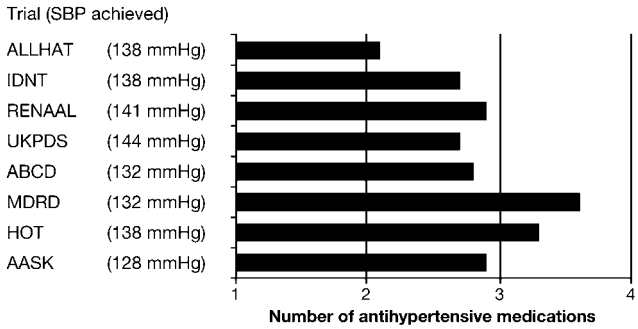

Figure 1 Average number of antihypertensive medications needed per patient to achieve target SBP goals (reprinted from Bakris GL).[57]

Improving patient compliance with medication

Poor compliance with prescribed medication also contributes to suboptimal hypertension control rates. Compliance is especially an issue among the elderly and patients with diabetes, as they are often required to take multiple medications in conjunction with antihypertensives. Medication compliance may be further complicated by the largely asymptomatic nature of hypertension. In clinical practice, treatment compliance may be as low as 50%,[74,75] which is much lower than that generally observed in the clinical trial setting where tighter controls and monitoring reduce non-compliance. Furthermore, in addition to issues regarding compliance with antihypertensive therapy, long-term persistence (remaining on therapy) is also problematic.[76]

Measures to improve patient compliance and persistence are therefore important components of the overall approach to treatment of hypertension. Such measures include: (1) simplifying the dosage regimen (e.g. minimizing both the number of tablets taken and the frequency of administration); (2) selecting drugs that are well tolerated (as outlined above) and (3) educating and motivating patients to ensure that they adhere to treatment.[74,75,77] Compliance and long-term persistence are linked with tolerability, which therefore adds to the importance of the choice of antihypertensive therapy.[58,75,78,79] Evidence from clinical trials suggests that higher levels of persistence are seen with ARBs than other classes of hypertensive drugs.[79,80] For example, in a usual-care setting, patients receiving valsartan relative to amlodipine or lisinopril were more compliant and persistent with pharmacologic therapy, independent of patient chronic disease burden.[81]

Monitoring for intake of BP-increasing substances and other modifiable factors

One other reason for patients failing to reach target BP has been identified as unanticipated intake of substances that may raise BP.[6] Such substances include prescription- or over-the-counter drugs (e.g.

corticosteroids, non-steroidal anti-inflammatory drugs, sympathomimetics in cold remedies), drugs of misuse and foods or herbal preparations (e.g. liquorice, 'herbal ecstasy' and St John's Wort).[6] It is also well known that excessive intake of alcohol can elevate BP,[6,82] although low-moderate alcohol intake may be protective.[83] Consequently, patients should be thoroughly questioned about their use of alcohol, other medications or herbal preparations.

Unsuspected 'secondary' causes of hypertension, such as renovascular disease, coarctation of the aorta, Cushing's syndrome, primary aldosteronism, etc., should also be considered in patients not responding appropriately to therapy, and addressed accordingly.[6]

Conclusions

Despite the availability of effective antihypertensive treatments and guidelines for their use, hypertension control rates remain suboptimal. Guidelines remain a valuable tool, and awareness and adherence to treatment guidelines and BP goals must be improved. It is imperative for physicians to select the most appropriate agents at relevant doses and implement pharmacotherapy early in order to reduce CV risk and prevent end-organ damage. As pharmacotherapy is a central component of hypertension treatment, physicians must be prepared to adopt a more aggressive treatment approach and appreciate the value of combination therapy in order to ensure that patients reach recommended BP goal in a timely manner. Angiotensin II receptor blocker/HCTZ fixed-dose combinations, such as valsartan/HCTZ, are efficacious, well-tolerated treatment options that should be exploited more in clinical practice. Treatment with such combinations may confer additional cerebrovascular, CV and renal protection in comparison with other antihypertensive treatment options.

The interaction between physicians and other health-care providers with patients should be used as an opportunity to reinforce messages about the risks of hypertension and the importance of treatment compliance and regular check-ups. Patients should be educated with respect to the seriousness of hypertension, despite its asymptomatic nature, and physicians should explain the detrimental long-term effects of the condition, such as irreversible organ damage, if left untreated. Physicians can also help improve patient compliance by monitoring patients for drug efficacy and adverse events. It is also essential to emphasize the importance of complementary lifestyle modifications and the associated positive impact they have on BP. Patients need to be made aware that management of hypertension does not just involve medication and that appropriate lifestyle changes are equally important.

It is hoped that these measures, taken together, will help translate the benefits of antihypertensive therapy seen in clinical trials into real-life clinical practice.

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