

EDUCATIONAL REVIEW

Hypertension

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Abstract

Hypertension is a common condition affecting one in four adults. It is a leading cause of cardiovascular morbidity and mortality and appropriate treatment strategies that are both clinically and cost effective are key to the management of this condition. Recent guidelines have focused on addressing total cardiovascular risk and recommended rational combinations of antihypertensives as well as highlighting the importance of lifestyle intervention. Recent advances have increased understanding of the pathogenesis of hypertension and have opened the possibility of novel interventions for treatment.

There remains no dispute that those with severe hypertension (greater than 220/120mmHg) require initiation of treatment without delay.² However, the majority of hypertensive patients can be observed for a period of weeks before a definitive decision regarding treatment is made. Blood pressure measurements above 140/90mmHg on three separate occasions or a strong family history of cardiovascular disease should prompt lifestyle advice to specifically target blood pressure reduction as well as general lifestyle interventions to reduce cardiovascular risk.

The Joint British Societies (JBS)³, British Hypertension Society (BHS)² and Scottish Intercollegiate Guidelines Network (SIGN)⁴ have produced consistent guidelines with regard to when to initiate pharmacological therapy (Figure 1). The decision to introduce pharmacological intervention in addition to lifestyle advice should be informed by total cardiovascular risk. The new Joint British Societies' Cardiovascular Disease (CVD) risk prediction charts are widely available and are based on established Framingham risk factors (smoking, age, sex, Blood Pressure and cholesterol).

Figure 1

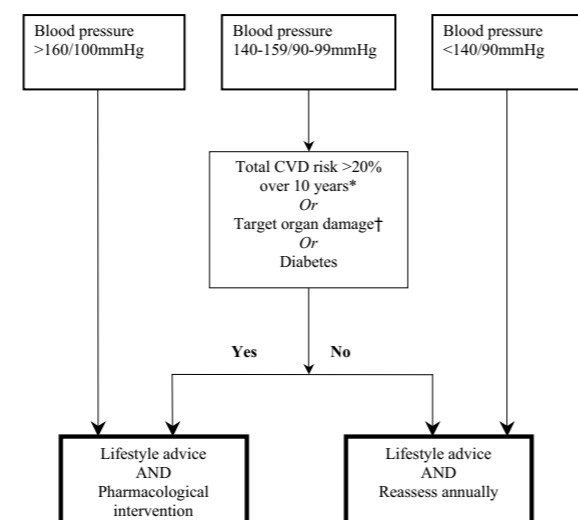


Figure 1

*Cardiovascular risk (CVR) determined by Framingham risk factors i.e. smoking, age, blood pressure, cholesterol, diabetes and LVH. Risk factor calculators are available online at:
<http://cvrisk.mvm.ed.ac.uk/calculator/framingham.htm>

†Target organ damage includes renal impairment, LVH, retinopathy.

High risk groups

The link between social deprivation and poor health is a well recognised phenomenon and is of particular relevance to Scottish practice⁵ where both cardiovascular disease and deprivation are commonly seen. Conventional risk calculations do not take into account deprivation and as a result, the risk among people from low socioeconomic groups is often underestimated.⁶ Recently published data demonstrated that using a scoring method that takes into account social deprivation as based on postcode, as well as family history, identifies more people at risk.⁷ This provides a useful tool to target treatment at those who will benefit most. The use of socioeconomic data to inform clinical decision making in this context has been endorsed by SIGN. A demonstration version of the risk calculator known as ASSIGN, which includes the Scottish Index of Multiple Deprivation score (based on postcode) as well as family history, quantity smoked and conventional Framingham parameters, is available online (<http://assign-score.com>).

It is recognised that there is a higher prevalence of cardiovascular disease amongst Asian patients and conventional charts will underestimate their risk by as much as 1.4.³ Other populations are known to be at increased risk and while earlier treatment is not advocated, they should be screened regularly and their overall risk assessed. These include women with a history of pregnancy induced hypertension, gestational diabetes and pre-eclampsia⁸ or who have experienced a premature menopause as well as patients with chronic inflammatory conditions such as rheumatoid arthritis.⁹ Modification of any lifestyle factors as well as careful screening using total cardiovascular risk charts should be routine. It should be remembered that although these conditions may increase relative risk, the absolute risk as based on risk calculations should be the basis of treatment.

The Elderly

The incidence of hypertension rises with age and elderly patients have the most to gain from blood pressure lowering, particularly with regard to reducing morbidity and mortality associated with cerebrovascular disease (i.e. while the relative benefit of blood pressure reduction is the same as in younger patients, absolute benefit is greater in the elderly as their risk of cardiovascular disease is higher.) The Swedish Trial in Old People with Hypertension (STOP) showed efficacy of antihypertensives with regard to cardiovascular morbidity and mortality in patients aged between 70 and 84 years.¹⁰ However, most randomised control trials examining the benefits of antihypertensives did not include patients over the age of 80 and there are concerns that treatment of hypertension in this age group is associated with an increase in non-cardiovascular mortality. A meta-analysis of antihypertensives in the over 80 age group has proved inconclusive with regard to overall mortality.¹¹ The Hypertension in the Very Elderly Trials (HYVET) study¹² is underway to assess the effect of management of hypertension in the over 80s and the results are awaited with interest. In the meantime, the advice remains that treatment should be continued in hypertensive patients when they reach the age of 80. However, in those in whom the diagnosis is made for the first time at the age of 80, the decision should be influenced by other co-morbidities.²

How to Treat?

A combined approach of lifestyle and pharmacological management where required is central to the treatment of

hypertension. Treatment should be to a target of 140/85 in non-diabetic patients with a stricter target of 130/80 in those with diabetes or end organ damage. There is little evidence around blood pressure targets using ambulatory blood pressure monitors. However, particularly in subjects where there is a suspicion that there is a discrepancy between home and clinic readings they can be useful. Targets for ambulatory monitoring should use mean daytime and night time readings and targets should be lower than office readings (i.e. by 10mmHg systolic/5 mmHg diastolic). While it is acknowledged that these targets are ambitious, there is no evidence of a threshold of effect down to at least 115/75mmHg¹³ and it is clear that the benefits of blood pressure reduction apply to across the spectrum, particularly in high risk patients.¹⁴

Lifestyle factors

Lifestyle factors which can contribute to blood pressure reduction include improved diet, aerobic exercise and reduced alcohol consumption as shown in Table 1.

Table 1

Intervention	Recommendation
Weight reduction	Maintain ideal body mass index (20–25 kg/m ²)
Diet	Consume diet rich in fruit, vegetables, low-fat dairy products with reduced content of saturated and total fat
Dietary sodium Restriction	Reduce dietary sodium intake to 100 mmol/day (2.4g sodium or 6g sodium chloride)
Physical activity	Engage in regular aerobic physical activity, for example, brisk walking for at least 30 min most days
Alcohol	Men < 21 units per week Women < 14 units per week

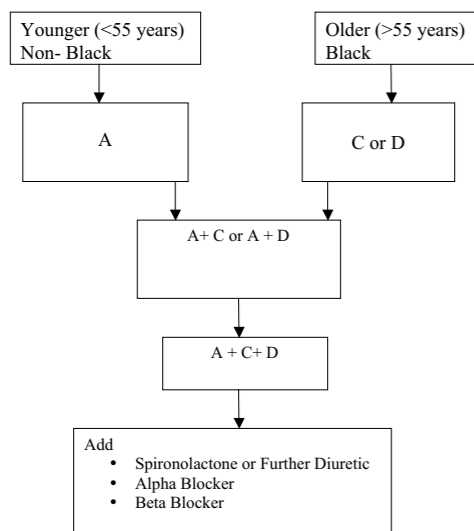
Placebo controlled studies have shown that reduced sodium intake lowers blood pressure and increases response to pharmacological therapy.^{15,16,17} However, until very recently, evidence of long term benefit was lacking. This has now been addressed in a recent major study from the USA¹⁸ where reduction in dietary sodium intake is associated with a reduced risk of cardiovascular morbidity and mortality. Thus it is clear that moderate salt reduction (maximum of 6g or 100mmol per day) should be part of healthy lifestyle advice as recommended by the UK Foods Standards Agency.

The interaction of potassium and sodium has been proposed as an important factor in the regulation of blood pressure. Epidemiological data provides support for this view in those societies with low sodium/ high potassium diets have lower blood pressure than industrialised societies.¹⁹ Potassium supplementation appears to reduce blood pressure²⁰ and the need for antihypertensive medication.²¹ In addition, the Dietary Approach to Stop Hypertension (DASH) trial²² demonstrated that a fruit and vegetable rich diet containing a potassium content more than twice that of an average American diet, reduced blood pressure to a greater extent than controls with a similar level of sodium.

Drug Treatment

Although lifestyle modifications can be effective,²³ pharmacological therapy is indicated in a large number of people with hypertension, around 850 000 patients in Scotland. In practice, most clinicians use the BHS guidelines to manage antihypertensive therapy a treatment strategy based around the classification of hypertension into high vs. low renin hypertension (Figure 2).²⁴

Figure 2:



This in turn reflects the fact that younger hypertensive patients tend to have renin levels in the high/normal range while older people have low renin levels. This concept of renin suppression in the older hypertensive population is consistent with the notion that subjects have a relative expansion of body sodium content. The mechanism that accounts for this is unclear; it is possible that resetting of the renal pressure/natriuresis relationship, partly as a consequence of hypertension, results in long term sodium retention. Alternative methods, including that action of aldosterone (see below) may also account for this phenomenon.

However, regardless of mechanisms, angiotensin converting enzyme (ACE) inhibitors, angiotensin II blockers and beta blockers are considered to be more effective in high renin hypertension²⁵ (more common in patients under the age of 55 years) based on their action on the renin- angiotensin-aldosterone system (RAAS) with diuretics or calcium channel blockers being a more appropriate choice in low renin patients²⁶ (black patients²⁷ and those older than 55 years), where the RAAS is already suppressed. The rationale is that if one class of drug is not effective, it should be combined with an agent from the other "arm" to maximise the sites of intervention. The guidelines have been revised in light of the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) trial which compared the combination of ACE inhibitor (perindopril) and dihydropyridine calcium channel blocker (amlodipine) with a beta blocker/thiazide combination (atenolol and bendrofluzide). The most significant revision in the guidelines has been a further caution of the use of beta blockers as first line agents for the treatment of hypertension.

The debate as to whether specific antihypertensives offer cardiovascular protection in addition to their blood pressure lowering effects continues. Data from the Anti Hypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)²⁸, published in 2002, suggested superiority (both in terms of blood pressure reduction and cardiovascular complications) of a diuretic based regime over calcium channel blockade and ACE inhibition, leading to advice that thiazides should be first line therapy in the majority of patients with hypertension. However, the results of ALLHAT may have been influenced by the large number of black participants who had a lower blood pressure drop and reduced protection from cardiovascular complications while receiving ACE inhibitors.²⁹ A subsequent meta analysis³⁰

published in 2003 (which included ALLHAT results) concluded that the major impact of intervention on cardiovascular complications were related to effective blood pressure reduction and not specific agents.

In the ASCOT trial, mentioned above, the primary endpoints of non-fatal myocardial infarction and fatal coronary heart disease were not reached but the amlodipine/perindopril combination was associated with a reduction in the secondary endpoints including cardiovascular mortality (-24%); fatal and nonfatal stroke (-23%); total cardiovascular events and procedures (-16%); and new-onset diabetes mellitus (-30%).

There was a small but statistically significant reduction in blood pressure associated with amlodipine and perindopril (2.7/2.9mmHg; $p < 0.0001$) as compared to atenolol +/- bendrofluzide. However, the benefits of the "newer" drug combination persist even following adjustment for the blood pressure difference.³¹ In addition to the cardiovascular outcome data, ASCOT confirmed previous reports³² of a 30% excess risk of developing diabetes associated with beta blockers.

The low dose diuretics used in this trial, are likely to have had minimal metabolic effects. In addition patients randomised to this arm also received potassium supplementation when required (hypokalaemia, commonly associated with diuretic use, blunts pancreatic insulin release). It can be concluded therefore, that the excess of new diabetes arose predominately from the use of beta blockade in the form of atenolol. The results seen in ASCOT³³ and others³² may not constitute a class effect and more cardio-selective beta blockers like bisoprolol and nebivolol not associated with an increase in peripheral vascular resistance, may prove more useful agents. As yet, there are no head to head studies to compare beta blockers but on the basis of current evidence, beta blockers should not be used as first line agents for the treatment of hypertension, unless there are other compelling indications i.e. ischaemic heart disease (IHD).

Additional treatment strategies

A significant minority of patients remain uncontrolled on three agents (A+ C+D) and their management can prove difficult. Simple interventions like fixed dose compound preparations of drugs may improve compliance. A search should be made for substances prescribed or over the counter (non-steroidal anti-inflammatories, "herbal" remedies) that may be having a deleterious effect on blood pressure control. Lifestyle advice should be reiterated as excess sodium intake may be a significant factor in limiting the antihypertensive action of drugs. In addition however, consideration should be given as to whether the patient may have a secondary cause for their hypertension (Table II).

In particular, recent recognition of the increased prevalence of aldosterone associated hypertension³⁴ provides a rationale for screening for relative aldosterone excess using the aldosterone to renin ratio (ARR). Interpretation of ARR can be problematic particularly if there is concomitant use of antihypertensives which cause suppression or elevation of the plasma renin activity (PRA) (Table III). Once an elevated ARR has been established, the question as to whether excess and autonomous aldosterone arises from an adrenal adenoma is raised; as a result, further investigation of possible primary aldosteronism should be within a secondary care centre. The potential benefit of these investigations lies in the fact that resistant hypertension due to idiopathic hyperaldosteronism can be effectively managed with addition of the aldosterone antagonist spironolactone.

Table II

Secondary Causes of Hypertension

Endocrine

Cortisol excess
Pheochromocytoma
Mineralocorticoid excess
Acrogomegaly
Hyperthyroidism
Hypothyroidism
Hyperparathyroidism

Renal

Renovascular disease
Renal parenchymal disease

Other

Coarctation of the aorta
Obstructive sleep apnoea

Table III

Drug	Plasma renin Activity	Effect on ARR
β-blockers	-	-
Diuretics	-	-
ARBs	-	-
ACE inhibitors	-	-
Calcium-channel blockers	- / -	- / -

There is accumulating evidence to support the use of low dose (25mg) spironolactone as a fourth line agent for resistant hypertension^{35,36} even in the absence of an elevated ARR based on recent recognition of the deleterious cardiovascular effects of aldosterone.^{37,38}

In conclusion, the choice of therapy in patients with hypertension, in whom treatment is indicated on the basis of their 10 year CVD risk, should be based on the BHS algorithm. In the presence of other specific indications, (IHD, microalbuminuria) appropriate alternatives should be initiated. The overwhelming requirement however, is to reach the required blood pressure target by adding further agents appropriately. Since only 40% of treated patients in the UK are on more than one antihypertensive,³⁹ it is unlikely that the number of patients achieving good blood pressure control will rise above the current level of around 50%.³ The emphasis on overall cardiovascular risk means that additional pharmacological therapy, including statins and aspirin should be introduced in order to address all possible areas of intervention.

New Perspectives

Pathogenesis

The aetiology of hypertension remains unknown in around 90% of patients and it is recognised that its aetiology reflects a

complex interaction of environmental/lifestyle and genetic factors. Rare, monogenic forms of hypertension are useful insights to possible mechanisms behind the development of hypertension in a wider context. Two examples include Glucocorticoid Remediable Hyperaldosteronism (GRA) and 11_β-hydroxylase deficiency. These disorders involve the genes that encode aldosterone synthase (which catalyses aldosterone production) and 11_β-hydroxylase gene (which encodes the enzyme responsible for cortisol production). A recent review of these and other rare monogenic forms of hypertension,⁴⁰ gives further details however nearly all cluster around the mechanisms of renal sodium retention, synthesis of aldosterone or action of aldosterone illustrating the importance of the locus in regulating salt and water balance and blood pressure. It is clear therefore, that these genes are plausible candidates for contributing to the population variation in aldosterone and cortisol production, and development of hypertension and cardiovascular disease.

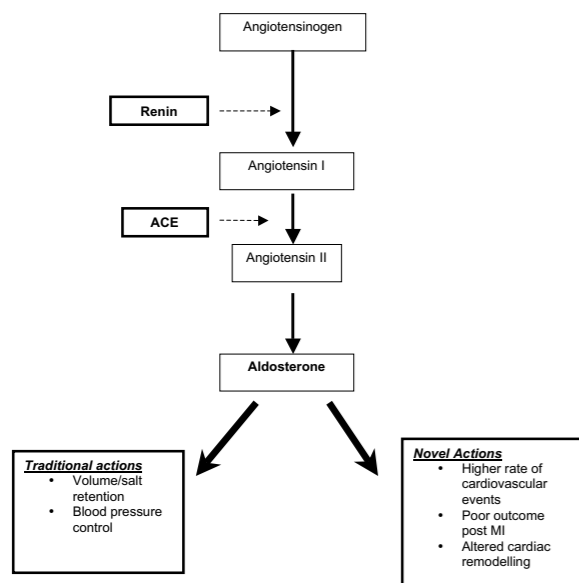
The British Genetics of Hypertension study (BRIGHT), one of the largest studies examining the genetics of hypertensive patients of white European ancestry, has identified 4 loci that may be implicated.⁴¹ However, the identification of specific causative genes has been more problematic. Recently, positive findings have emerged from analysis of the BRIGHT cohort with regard to the WNK1 gene. This gene encodes a serine-threonine kinase and is involved in the Na-Cl channel in the terminal segment of the collecting duct; clearly a crucial area in salt balance and consequently blood pressure control. Mutations in WNK1 have recently been found to be implicated in Gordon's syndrome, or pseudohypoaldosteronism type II, a rare monogenic form of hypertension.⁴² A single nucleotide polymorphism near the promoter region of WNK1 has been associated with severity of hypertension in the BRIGHT population.⁴³ Further genetic analysis from the BRIGHT cohort has highlighted the importance a region on chromosome 8 which encodes aldosterone synthase and 11 beta hydrogenase. As previously mentioned, these genes encode the enzymes which catalyse the terminal steps in production of aldosterone and cortisol respectively. There is a high degree of linkage across this loci and a number of polymorphisms are commonly "co-inherited" to produce common haplotypes. Very recent data suggests that the haplotype combination of -344C (a polymorphism in the promoter region) and intron 2 is highly significantly associated with reduced risk of blood pressure (odds ratio of 0.8). (Personal communication; Padmanabhan S et al).

Treatment

Until recently, the focus of intervention has centred on inhibition of angiotensin (ACE inhibitors, A2 blockers). However, the principal human mineralocorticoid hormone aldosterone, the end product of this system, has traditionally not received the same attention as a therapeutic option. Its role in cardiovascular disease in general, as well as in hypertension more specifically, has received new interest as a result of recent studies. In addition to the traditional functions of aldosterone (electrolyte balance, control of blood pressure) there is increasing awareness of its effects on vascular reactivity, the progression of Left Ventricular Hypertrophy (LVH) and fibrosis and its role in inflammation and vascular oxidative stress (Figure 3).

The previously underestimated frequency of relative aldosterone excess, identified by an increased ARR⁴⁴ underlines the important role of aldosterone in relation to the development of hypertension. It is clear that levels of aldosterone, even within the normal range, predict future hypertension⁴⁵ and in the

Figure 3



context of a renewed focus in reducing total cardiovascular risk, studies have demonstrated the deleterious effects of aldosterone excess. Milliez et al⁴⁶ carried out a comparison of the cardiovascular events experienced by a group with primary aldosteronism (PA), with those with essential hypertension. The PA group had an excess of Cerebro Vascular Accident (CVA) (OR 4.2; 95% CI 2.0 to 8.6) and non-fatal Myocardial Infarction (MI) (OR 6.5; 95% CI 1.5 to 27.4).

This has been further emphasised by the Randomised Aldactone Evaluation Study (RALES)⁴⁷ which led to a change in practice both in the management of heart failure patients as well as an increased recognition of the wider benefits of aldosterone blockade. One thousand six hundred and sixty three patients with moderate to severe heart failure were randomised to conventional therapy (ACE inhibitor, loop diuretic and digoxin) or conventional therapy plus low dose (25mg) spironolactone. The trial was stopped early due to an excess of deaths in the control group. There was a 30% reduction in total mortality in the treatment group versus the placebo, mainly attributed to sudden cardiac deaths. In addition, there were lower rates of hospitalisation and an improvement in symptoms of heart failure among those treated with spironolactone.

The benefits of aldosterone blockade have been further supported by Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)⁴⁸ where six thousand six hundred patients with acute MI complicated by heart failure received optimal medical management plus the highly selective aldosterone antagonist eplerenone or placebo. Morbidity and mortality data supported the use of aldosterone blocking therapy. Finally, the 4E LVH study⁴⁹ examined the effect of enalapril alone, eplerenone alone and the combination of enalapril and eplerenone on measurements of LVH in hypertensive patients. Aldosterone blockade alone was superior to angiotensin converting enzyme inhibition alone however the maximal left ventricular mass regression was seen in the combination of eplerenone and enalapril.

Thus, while there is a large body of evidence to support the opinion that the size of blood pressure reduction is the major influence on reducing cardiovascular events, the above studies also suggest a key role for suppression of the RAAS and aldosterone over and above blood pressure differences.

Conclusion

The management of hypertension and cardiovascular disease remains a challenge to physicians both in primary and secondary care. Despite significant advances in understanding and therapeutics a large proportion of patients continue to be exposed to the deleterious effects of uncontrolled blood pressure. The overriding need is for better adherence to blood pressure targets following the JBS/BHS guidelines in the context of reducing total cardiovascular risk. Exciting new prospects are on the horizon with the aim to reduce further cardiovascular complications, possibly with effect in addition to blood pressure reduction.

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Educational Review Questions

- 1) 45 year old male with a blood pressure of 150/95. TC: HDL slightly elevated. He is a non-smoker, with a strong FH of premature CAD and hypertension. He received lifestyle advice 2 months ago. The most appropriate next step would be:
 - a) Continue lifestyle advice. No treatment
 - b) Titrate ACE inhibitor to target BP of <140/80
 - c) Titrate ACE inhibitor to target BP of <130/80
 - d) Thiazide with a target of BP 140/80
- 2) 60 year old female Type 2 Diabetic. She has stable ischaemic heart disease and her BP is 155/95. Drug history is as follows: Atenolol 25mg bd, aspirin 75mg, simvastatin 40mg. The optimum next treatment would be:
 - a) ACE to BP <140/80
 - b) ACE to BP <130/80
 - c) Thiazide to BP 140/80
 - d) Titrate up beta blocker until BP <130/80
- 3) 55 year old man with essential hypertension and a BP of 160/95 and a history of impaired glucose tolerance. Drug history is as follows: ramipril 10mg, amlodipine 10mg, bendrofluazide 2.5mg. It would be most appropriate to add
 - a) Atenolol 25mg bd
 - b) Lisinopril and titrate to target BP
 - c) Spironolactone 25 mg
 - d) Doxazosin 4mg
- 4) Action of antihypertensives on RAAS. Please answer True or False
 - a) Beta blockers elevate ARR
 - b) Ace inhibitors and angiotensin receptor blockers reduce renin levels
 - c) Diuretics do not affect ARR
 - d) Patients require to be off all antihypertensive medication for 3 days prior to ARR measurement.

ANSWERS ON PAGE 54