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UPDATE ON HYPERTENSION

SUMMARY

-  Hypertension is a major modifiable risk factor in the development of cerebrovascular disease, ischaemic heart disease, cardiac and renal failure
-  Reduction of blood pressure (BP) is more important than the choice of agent although individual agents are preferable in certain settings
-  Effective treatment leads to a 42% reduction in the risk of stroke and a 21% reduction in cardiovascular mortality, but international studies continue to show that there is substantial under-diagnosis, inadequate treatment and poor rates of BP control
-  The majority of patients (>50%) require more than one drug to control BP ($\leq 140/90$ mmHg)

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, with two-thirds of the cerebrovascular disease burden and half the ischaemic heart disease burden being attributable to non-optimal BP.¹ In Ireland in 2000, CVD was the number one killer and was responsible for 41% of all deaths.²

Normal BP 120/80mmHg is the product of cardiac output and peripheral resistance.³ Hypertension (HTN) is a sustained increase in either one of these factors or both. HTN affects up to 50% of middle-aged and older people.⁴ As it has no reliable symptoms or signs, routine screening in clinical practice is essential. Diastolic BP (DBP) peaks at approximately 60 years of age in men and 70 years in women and thereafter gradually falls, whereas systolic BP (SBP) rises throughout adult life.⁴ Over 30% of persons over 80 years of age have isolated systolic hypertension (ISH).⁵

The majority of patients have essential or primary HTN (>90%) with cause unknown. Secondary HTN is uncommon and may be related to renovascular disease, hyperaldosteronism (10-20% of resistant HTN), Cushing's syndrome, coarctation and medications (NSAIDs, OCP, steroids, cocaine, amphetamine and erythropoietin).⁶

Despite many guidelines, international figures demonstrate that BP is controlled to the target of 140/90mmHg in less than 10% of patients and that the majority (60%) of patients are treated with monotherapy.^{7, 8, 9, 10}

RISK FACTORS AND COMPLICATIONS

Contributory factors for HTN include obesity, heavy alcohol intake (>3units/day), high salt intake, lack of exercise and environmental stress. Hypertension is a risk factor for stroke, myocardial infarction, renal failure, congestive heart failure, progressive atherosclerosis and dementia. There is a continuous, graded relationship between HTN and the risk of CVD.⁶ Systolic pressure is a stronger predictor than DBP of cardiovascular events in patients over 60 years of age, with ISH associated with higher morbidity and mortality.¹¹ Dyslipidaemia, diabetes mellitus (DM), increasing age, cigarette smoking and a family history of CVD, as well as HTN add to a persons' increasing risk of CVD. Estimation of CVD risk is easily done using risk assessment charts with those at high risk defined as those whose 10 year risk of fatal CVD is $\geq 5\%$ (equivalent to a 20% risk of any CVD event) or will exceed 5% if projected to age 60 years.¹²

DIAGNOSIS

All adults should have their BP measured routinely every 5 years.¹³ Annual readings should be taken in those with high-normal values and those who have had high readings at any time in the past. The 2003 European Society of Hypertension – European Society of Cardiology¹⁴ classification of BP values, which are similar to the WHO guidelines¹⁵, is outlined in Table 1. A diagnosis of HTN should be based on multiple *clinic* readings taken on separate occasions with the interval between readings based on the degree of elevation (slight elevation: months, marked elevation: weeks).

Category	Systolic BP mmHg	Diastolic BP mmHg
Optimal	< 120	< 80
Normal	< 130	< 85
High normal	130 – 139	85 – 89
Hypertension Mild / Grade 1	140 – 159	90 – 99
Hypertension Moderate / Grade 2	160 – 179	100 – 109
Hypertension Severe / Grade 3	≥ 180	≥ 110
Isolated Systolic Hypertension	≥ 140	< 90

*Table 1. Definition and classification of blood pressure values**

*Classification based on clinic values.¹⁵ If a patient's systolic and diastolic BP fall into different categories, the higher category should apply.

Ambulatory BP measurements (ABPM) provide additional information on BP profiles over 24 hours. Routine use of ABPM is currently not recommended but it is important in certain circumstances such as the identification of white coat HTN, and in the treatment of patients with considerable variability in their readings or those with resistant hypertension. Home measurement devices are useful provided they are accurate, well maintained and do not create excessive anxiety or induce self-modifications of a planned treatment regimen. Ambulatory and home BP values tend to be lower than clinic levels, so threshold and treatment targets need to be adjusted downwards. Clinic values of 140/90 mmHg are equivalent to 24-hour average values of 125/80 mmHg and home measurements of 135/84mmHg.¹⁵

INVESTIGATIONS

All hypertensive patients should have a thorough history and physical examination, assessing for evidence of target organ damage and potential causes of secondary HTN. Routine investigations should include urinalysis (protein and blood), serum creatinine and electrolytes, blood glucose, serum total and HDL cholesterol and ECG. Specialist opinion may be indicated for patients with severe hypertension, impending complications (transient ischaemic attack, left ventricular hypertrophy), HTN in young age (<40years), resistant HTN, treatment resistance (to > 3 drugs), multiple drug intolerance or contraindications, persistent non-compliance and HTN in pregnancy.¹³

TREATMENT

The goal of treating HTN is to achieve the maximum reduction in the total risk of cardiovascular morbidity and mortality. This requires the reduction of BP levels to specific targets and the treatment of all the reversible risk factors identified.

Nonpharmacological Measures

Weight reduction, reduction of excessive alcohol intake (to <21 units/wk for men and to <14units/wk for women), reduction of salt intake (to <5g/day ≈ 1 teaspoon), decrease in saturated and total fat intake, an increase in fruit and vegetable consumption and regular dynamic physical exercise all lower BP. Additional factors that reduce CVD risk include cessation of smoking, replacement of saturated fats with mono-unsaturated fats and increased oily fish consumption. All patients should be educated regarding these measures. Effective implementation of these measures requires enthusiasm, knowledge, patience, and considerable time. It should also be backed up with simple clear written information. If drug therapy is indicated, all these measures should be continued in parallel. Details on the management of obesity and smoking cessation are available in previous NMIC bulletins (Vol 8 (2) 2002, Vol 7(2) 2001).

Pharmacological Measures

Benefits: Many randomised controlled trials (RCTs), overviews and meta-analyses confirm the significant reduction in mortality (all cause and cardiovascular), cerebrovascular accidents and coronary events associated with antihypertensive therapy.^{5,15-19} Table 2 shows the percentage risk reduction in these events achieved by controlling HTN and ISH, and the significance of achieving target BP values of 140/90mmHg.¹⁸⁻²⁰ Optimal cardiovascular outcome is linked with *the level of BP control*, rather than the actual drug class used to achieve control.¹⁸ These outcome trials have shown that drug therapy is associated with significant clinical effects: a 42% reduction in stroke, a 14% reduction in coronary events and a 21% reduction in cardiovascular mortality.

Table 2. Relative risk reduction of fatal events and combined fatal and non-fatal events in patients on active anti-hypertensive treatment versus placebo or no treatment and the effect of the intensity of treatment.

	Systolic-diastolic HTN Risk reduction with treatment	Isolated systolic HTN Risk reduction with treatment	Achieving target BP of 140/90mmHg Risk reduction with treatment
Mortality			
All cause	-14%	-13%	-4%
Cardiovascular	-21%	-18%	-7%
Fatal and non-fatal events			
Stroke	-42%	-30%	-23%
Coronary	-14%	-23%	-15%

When to initiate treatment?

Initiation of treatment is based on two criteria: the levels of SBP, DBP and the total level of CVD risk (calculated using CVD risk assessment charts).

Those with *high normal* BP benefit from pharmacological therapy if there is coexisting history of stroke, coronary artery disease or diabetes mellitus. Those with *grade 1/2 HTN* have been shown to benefit from pharmacological therapy, with the benefits greatest in those with a 10-year risk of fatal CVD of ≥ 5%.

In those with *Grade 3 HTN*, drug therapy should begin immediately as well as an assessment for other risk factors and advice regarding lifestyle measures.

The major drug classes available are:

Thiazide diuretics: Anti-hypertensive effect is via a complex series of mechanisms, not directly related to the diuretic potential. It is gradual in onset and persists for up to 24 hours. Recognised adverse effects include erectile dysfunction (reversible on discontinuation) and minor biochemical disturbances. High doses cause more marked changes in plasma potassium, uric acid, glucose (particularly in combination with a β blocker), and lipids, with no advantage in blood pressure control and should not be used. Diuretics should be avoided in patients on lithium therapy and those suffering from gout.

Beta-blockers: Antagonise the effects of the sympathetic nervous system and circulating catecholamines. Acutely they reduce cardiac output via blockade of β_1 cardiac receptors; chronically their effect is via a reduction of peripheral vascular resistance via suppression of sympathetic activity and decreased renin release. They are more effective in younger patients and less effective in black patients. Adverse effects include bradycardia, cold hands and feet, worsening of symptoms of peripheral vascular disease and Raynaud's syndrome, CNS effects (impaired concentration and memory, vivid dreams, these are less frequent with the water soluble beta-blockers), aches in limbs, fatigue during exercise and metabolic effects (increased triglycerides, reduced HDL cholesterol). They are contraindicated in asthma.

Calcium channel blockers (CCBs): The longer-acting dihydropyridine CCBs (nifedipine (modified release), amlodipine) are selective at blocking calcium channels in vascular smooth muscle cells, resulting in reduced peripheral resistance and BP. Nondihydropyridine agents (diltiazem, verapamil) block calcium channels in cardiac myocytes reducing cardiac output. Side effects of the dihydropyridine CCBs include peripheral oedema (dose dependent), flushing and headache. The nondihydropyridine CCBs have negative inotropic and chronotropic effects and should be avoided in patients with heart failure and used with caution in combination with beta-blockers.

Angiotensin Converting Enzyme (ACE) inhibitors: Inhibit the conversion of angiotensin I to angiotensin II by inhibiting ACE, resulting in vasodilation and a reduction in BP. Adverse effects include hypotension (may be profound after the first dose, especially in those with an activated renin-angiotensin system [heart failure, accelerated HTN and renovascular disease]), persistent dry cough (10-15% users), hyperkalaemia (caution with co-prescription with potassium-sparing diuretics or NSAIDs), and angioneurotic oedema. They are contraindicated in patients with renovascular disease and should be avoided in women of childbearing potential.

Angiotensin receptor antagonists (ARBs): Block type 1 angiotensin II receptors, leading to vasodilatation and a fall in BP. They have similar indications, efficacy, cautions and side effects as ACE inhibitors, but have a reduced incidence of cough and angio-oedema due to the lack of an effect on the kinin system.

Alpha-blockers: Selectively block α_1 receptors, which are responsible for noradrenaline-mediated vasoconstriction, with resulting reduction in peripheral resistance and vasodilatation. They are generally used in combination with other agents, particularly in patients with concomitant problems (prostatism, type II DM, dyslipidaemia). They have modest lipid profile benefits (i.e. reduce total cholesterol, LDL, total triglycerides and increase in HDL). Short acting agents are associated with postural hypotension.

Centrally acting agents: Act at presynaptic α_2 receptors in the brainstem to reduce sympathetic outflow, leading to vasodilatation. Methyldopa is used in pregnancy, but otherwise they are rarely used as they are poorly tolerated.

Other vasodilators: Hydralazine, minoxidil and sodium nitroprusside all directly relax smooth muscle and can rapidly reduce BP. Should be reserved for use under hospital supervision to treat hypertensive crisis.

For each class of drug there are compelling indications and contraindications as well as possible indications, contraindications, and cautions for specific patient groups.¹³ These are outlined in Table 3.

Table 3. Compelling and possible indications, contraindications and cautions for the major classes of antihypertensive drug

Class of Drug	Compelling Indications	Possible indications	Possible Contraindications	Compelling Contraindications
Thiazide diuretics	Elderly, ISH, Heart failure		Erectile dysfunction	Gout
Beta-blockers	Angina, MI	Heart failure	Heart failure, PVD*, diabetes	Asthma / COPD Heart block
ACE-inhibitors	Heart failure, LV dysfunction, Type I diabetic nephropathy	Chronic renal disease Type II diabetic nephropathy	Renal impairment	Renovascular disease Pregnancy
ARBs	ACE inhibitor induced cough, Type 2 diabetic nephropathy	Heart failure Intolerant of other agents	Renal impairment	Renovascular disease Pregnancy
Alpha-blockers	Prostatism		Postural hypotension Heart failure	

PVD*- Peripheral vascular disease

What class of drug do you use?

The growing body of evidence from RCTs, overviews and meta-analyses is that the main benefit of BP lowering therapy is BP lowering per se and that there is little evidence of additional drug class-specific benefits with regard to major cardiovascular outcomes.^{13, 15, 18, 21}

The choice of drugs is influenced by many factors, including: a) the cardiovascular risk profile of the individual patient, b) the presence of target organ damage, clinical cardiovascular disease, renal disease or diabetes, c) the previous experience (favourable or unfavourable) of the patient with a given class of compounds, d) the presence of other coexisting disorders that may either favour or limit the use of particular classes of drugs, e) the costs of drugs (diuretics being by far the least expensive drugs available) and f) the possibility of interactions with drugs used for co-existing conditions.^{6, 13, 15, 16, 18}

The British Hypertension Society (BHS) recently published a treatment algorithm (ABCD) that is designed to encourage improved BP control and is outlined in Table 4.²¹ The basis of the ABCD algorithm is that HTN can be broadly classified as “high renin” or “low renin” and is best initially treated by one of two categories of drugs, i.e. those which inhibit (ACE inhibitors, ARBs or beta-blockers) and those which do not inhibit (CCBs or diuretics) the renin-angiotensin system. An interval of at least 4 weeks should be allowed to observe the full response of any drug before moving to the next step.

Table 4. The BHS ABCD algorithm for combining BP lowering agents

	YOUNGER (<55YR) AND NON-BLACK	OLDER (>55YR) OR BLACK
Step 1	ACE inhibitor / ARB or (B) β-blocker	CCB or Diuretic
Step 2	ACE inhibitor / ARB or (B) β-blocker + CCB or Diuretic	
Step 3	ACE inhibitor / ARB + CCB + Diuretic	
Step 4	(Resistant HTN)	Add: either alpha-blocker or spironolactone or other diuretic

How many drugs do you use?

However many it takes to get the BP under control! Less than 50% of patients are controlled by monotherapy and more than two-thirds need a combination of two or more drugs to achieve optimal control.^{21,22} Rational combinations are outlined in Table 4. It has been noted that combination therapy involving β-blockers and diuretics may induce more new onset diabetes compared with other combinations, with the ACE inhibitors and ARBs notably inducing less diabetes.

Targets of treatment?

The current recommendation is that BP, both systolic and diastolic, be *intensively* lowered to at least below 140/90 mmHg and to lower values if tolerated, and to below 130/80 mmHg in diabetics.^{4,13,15,18,21,23}

How long do you treat for?

Antihypertensive therapy is generally for life.

SPECIAL PATIENT GROUPS

HTN in the elderly is common and is associated with a significant increase in cardiovascular morbidity and mortality, even in the very elderly (>90yr).^{5,24} The diagnosis of HTN may be difficult as older people show greater variation in BP and have a high prevalence of postural hypotension. Multiple measurements (both seated and standing) on several occasions are necessary to confirm the diagnosis. While all patients should be advised about the non-pharmacological measures, the majority require therapy and will require two or more drugs¹⁵. The majority have *isolated systolic hypertension (ISH)* which occurs as a result of progressive arteriosclerotic changes in the media of the aorta and its branches leading to arterial stiffening, causing a rise in SBP. SBP is a stronger predictor of all-cause mortality, coronary heart disease and stroke than DBP.⁵ At present ISH is underdiagnosed, undertreated and often poorly controlled.^{25,26} Therapy of ISH is associated with a significant reduction in cardiovascular events.^{5,11,20,22,27,28} Initiation of therapy should be particularly gradual, especially in frail individuals. Thiazide diuretics and the dihydropyridine CCBs are particularly effective in older patients and in those with ISH.^{11,20}

Diabetics with HTN: The co-existence of HTN and DM (either Type I / II) substantially increases the risk of macrovascular complications, including stroke, coronary heart disease, congestive heart failure and peripheral vascular disease and increases cardiovascular mortality. The development of HTN may reflect the onset of diabetic nephropathy in Type I diabetics. In both Type I and II, the threshold for starting treatment is BP ≥ 140/90 mmHg, the target is < 130/80 mmHg, or lower if proteinuria is present.^{13,15,23} While consensus regarding optimal first-line therapy is lacking, evidence supports the use of many drugs particularly the ACE inhibitors and the ARBs.^{15,23} In practice, many patients require three or more drugs to attempt HTN control.²⁹ Maintaining normal BP with the use of ACE inhibitors and ARBs reduce the rate of decline in renal function.

HTN in pregnancy occurs in 7-15% of pregnancies and is an important cause of maternal and perinatal morbidity and mortality. It should be treated in conjunction with specialist support.³⁰

TREATMENT OF ASSOCIATED RISK FACTORS

The use of aspirin and statins in high-risk patients (>5% 10 year risk of fatal CVD) and for the secondary prevention of cardiovascular disease is recommended^{13,15} and has been discussed in a recent NMIC bulletin (Vol 8 (6) 2002).

CONCLUSION

Hypertension remains a leading cause of cardiovascular morbidity and mortality.^{1,21} While there is a high awareness of the guidelines available for the management of HTN, greater efforts need to be made to implement them in clinical practice. With the array of effective medications available, knowledge of their effects (beneficial and detrimental) and our increased understanding of the benefit of intensive therapy, this condition warrants a continued, intensive and dedicated approach.

References available on request. Date prepared: Feb. 04

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet or summary of product characteristics (SPC) for specific information on drug use.

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**Added in BHS guidelines for HTN management 2004: summary
BMJ 2004; 328: 634-40 with accompanying editorial**