





UPDATE ON HYPERTENSION

-  **Hypertension is a major preventable cause of premature death**
-  **Diagnosis should be based on multiple clinic blood pressure (BP) readings, supported by ambulatory BP monitoring or home BP monitoring**
-  **Management of hypertension must take into account the overall cardiovascular risk and target organ damage as well as the BP readings**
-  **Use of more than one drug is necessary to achieve target BP in the majority of patients**

INTRODUCTION

Hypertension is recognised as one of the most important preventable causes of premature death worldwide.¹ It is reported to contribute to approximately half of all cardiovascular (CV) disease and is the single most important risk factor for stroke.¹ Blood pressure (and systolic blood pressure (SBP) in particular), tends to rise with age;² therefore because of increasing life expectancy in many countries, hypertension constitutes a major public health issue.^{1,3} A recent survey undertaken in Ireland found that 60% of study subjects aged ≥ 45 years had high blood pressure (defined as $\geq 140/\geq 90$ mmHg).⁴ Of these, 57% were not on any anti-hypertensive medication, while 70% of those on medication were not controlled adequately (i.e. to blood pressure $< 140/90$ mmHg). This bulletin will outline the currently recommended management strategies for hypertension.

DIAGNOSIS AND CLASSIFICATION OF HYPERTENSION

The diagnosis and classification of hypertension includes (1) establishing blood pressure (BP) levels, (2) identifying secondary causes of hypertension if present and (3) evaluating the overall CV risk and extent, if any, of BP-related target organ damage, all of which impact on the management strategy to be used.⁵

Blood Pressure Measurement: BP shows large spontaneous variations both during the day and between days and months; it is also affected by environmental changes such as posture, ambient temperature and pain / discomfort.^{5,6} For many years, BP was measured using a brachial pressure cuff with manual auscultation of the brachial artery.^{7,8} More recently, automatic BP measuring devices are used in the clinic and home settings. Ambulatory BP monitoring (**ABPM**) involves the subject wearing an appropriately sized cuff connected to electronic sensors which enables 24-hour evaluation of SBP and diastolic BP (DBP).⁶ Studies have reported that ABPM is associated with a prediction of CV risk greater than, and additional to, that provided by single BP readings; however, there may be difficulties with its use in patients with arrhythmias.^{6,9} Home BP monitoring (**HBPM**) also provides multiple BP measurements and is useful in measuring the subject's true BP levels. Both ABPM and HBPM are particularly useful in the diagnosis of **white coat hypertension** i.e. normotensive individuals whose BP appears elevated or those whose hypertension appears worse than it actually is, when measured by a healthcare professional.^{9,10} These subjects risk either receiving unnecessary anti-hypertensive medication or receiving excessive doses of such medication respectively. HBPM may also improve medication adherence in some patients.⁶ A recent review of relative effectiveness of all 3 modalities of BP monitoring suggested that more widespread use of ABPM for the diagnosis of hypertension would result in more appropriately targeted treatment.¹¹ It is important that all equipment (including cuffs, tubular connections, valves etc) used to measure BP is validated to acceptable standards and is kept in good working order.⁶

Table 1 outlines the European Society of Hypertension (ESH) Classification of Hypertension

Table 1: Definition and classification of blood pressure (BP) values*

Category	Systolic BP mmHg**		Diastolic BP mmHg**
Optimal	< 120	and	< 80
Normal	120 – 129	and/or	80 – 84
High Normal	130 – 139	and/or	85 – 89
Grade 1 Hypertension ***	140 – 159	and/or	90 – 99
Grade 2 Hypertension	160 – 179	and/or	100 – 109
Grade 3 Hypertension	≥ 180	and / or	≥ 110
Isolated Systolic Hypertension	≥ 140	and	< 90

*European Society of Hypertension classification of hypertension (2007), based on multiple BP readings⁵

**if a patient's SBP and DBP fall into different categories the higher category should apply for quantification of total CV disease risk

***Grades 1, 2, 3 correspond to classification of mild, moderate and severe hypertension respectively.

In the clinic setting, **the diagnosis of hypertension should be based on multiple BP readings.** The UK National Institute for Health & Clinical Excellence (NICE) recently recommended that clinic BP should be measured in both arms initially and if the difference in readings between arms is > 20 mmHg on repeated measurement, the arm with the higher readings should be used for all subsequent BP recordings.⁶ If the BP is $\geq 140/90$ mmHg and a second measurement is substantially different from the first, a third measurement should be taken and the lower of the last two measurements used. NICE also recommends ABPM (or HBPM if ABPM is not tolerated) where clinic BP is $\geq 140/90$ mmHg. At least two ABPM measurements per hour should be taken during the person's usual waking hours e.g. between 8am and 10pm. The average value of at least 14 such measurements is taken as the level for diagnosis.¹² **It should be noted that cut-off levels for treatment of hypertension are lower with ABPM and HBPM readings: an average of 135/85mmHg with ABPM / HBPM equates to an average of 140/90mmHg from multiple BP readings.**⁶

Secondary Hypertension: Up to 90% of patients have primary hypertension, for which no identifiable cause is found. For the remainder, there is an underlying cause as outlined in Table 2.

Table 2: Causes of Secondary Hypertension^{5,6}

Cause	Comments
Chronic kidney disease (parenchymal disease / renovascular hypertension)	Onset at <40 years +/- sudden onset +/- ≥grade 3 disease; ↑ urea; ↓ GFR; urinary abnormalities.
Hyperaldosteronism	Leads to Na ⁺ retention; ↓K ⁺ may be present. Thought to be associated with 10-20% of resistant hypertension.
Phaeochromocytoma	Facial flushing, ↑↑ HR, sweating, ↑ glucose. Due to massive release of catecholamines from adrenal glands.
Medication	Includes NSAIDs, MAOIs, mineralocorticoids, anti-Parkinson drugs, OCP, sympathomimetics, stimulants (e.g. cocaine).
Cushing's syndrome	Sudden ↑ weight; ↑ glucose; moon face; central obesity.
Thyroid disorders / acromegaly	↑ BP occurs in association with other classical signs and symptoms of the individual condition.
Obstructive sleep apnoea/ coarctation	

GFR = glomerular filtration rate; HR = heart rate; Na⁺ = sodium; K⁺ = potassium; NSAIDs = non-steroidal anti-inflammatory drugs; MAOIs = monoamine oxidase inhibitors; OCP = oral contraceptive pill

Secondary hypertension is more likely to be present when hypertension occurs in younger patients (aged <40 years) or in those with accelerated hypertension or those not responding to optimal anti-hypertensive treatment.⁶ **The commonest causes of secondary hypertension are renal parenchymal disease followed by renovascular hypertension.**⁶ These can usually be detected on clinical history, physical examination and routine laboratory tests. If renovascular hypertension is suspected this should be confirmed if possible via angiography to ensure that appropriate pharmacotherapy is instituted.¹³ For the rarer causes of hypertension, specialist referral is necessary to undertake the investigations needed for confirmation of the diagnosis and to institute appropriate medical or surgical treatment.

BP and Cardiovascular Risk: Although hypertension is formally defined as SBP levels of ≥140mmHg and/or DBP of ≥90mmHg (Table 1), epidemiological studies have shown a direct linear relationship between the level of BP and the occurrence of CV events, including cerebrovascular disease, coronary heart disease, heart failure, peripheral vascular disease, as well as renal failure, in both men and women.^{14,15} **It is estimated that there is a doubling of the risk of CV disease for every 10 point increase in DBP or every 20 point increase in SBP.**¹ Therefore, the threshold for a diagnosis of hypertension requiring pharmacotherapy should be considered as flexible, based on the overall CV risk.⁵

Hypertension, abnormal blood lipids, obesity and smoking are regarded as the key risk factors for CV disease.¹⁶ Other modifiable risk factors include lifestyle choices (e.g. diet, physical inactivity) psychosocial factors (e.g. social isolation, stress, low socio-economic status) and diabetes mellitus.¹⁴ Non-modifiable risk factors include age, gender, ethnicity, family history.¹

Signs of organ damage should also be sought at the time of diagnosis of hypertension. **Damage may be present in the heart, kidneys or arterial system.** ECG, urinalysis for evidence of microalbuminuria and physical examination, including fundoscopy, to look for evidence of vascular involvement are useful in evaluating potential organ involvement and for determining total CV risk.^{5,6}

Risk models / charts are available (e.g. the EU Systematic COronary Risk Evaluation (SCORE) risk chart to estimate an individual's CV risk using these risk factors in order to determine when and how to treat elevated BP.^{14,17} **HeartScore**, the web based version of SCORE, may be accessed, free of charge, at: <http://www.heartscore.org/Pages/welcome.aspx> (registration necessary).

MANAGEMENT OF HYPERTENSION

Treatment of hypertension is related to the grade of hypertension, the patient's estimated CV risk and the presence or absence of target organ damage.¹⁴ Management involves both non-pharmacological and pharmacological modalities.

Non-Pharmacological Management

All patients should be offered education and advice on lifestyle activities such as diet (including advice on weight reduction, salt intake and caffeine consumption) and alcohol intake (to within recommended limits), and they should be advised to increase physical activity.^{1,15} Epidemiological studies have identified an association between these lifestyle choices and elevated BP.^{1,15} In addition, all patients should be offered specific advice and help (including pharmacotherapy if required) to stop smoking because of its known link with increased CV risk.¹² **It is important that ongoing support is offered and the advice on lifestyle and weight is repeated at regular intervals to ensure continued compliance.**

Pharmacological Management

The major drug classes that are currently recommended for use in the pharmacotherapy of hypertension are outlined in Table 3.

Table 3: Details of Major Drug Classes Recommended for Use in Hypertension^{5,6,19-25}

Drug Class	Mechanism of Action	Clinical Comments	ADRs
ACEI (Angiotensin Converting Enzyme Inhibitor)	Suppression of Renin-Angiotensin-Aldosterone (RAA) System	BP ↓ of ~ 11/6mmHg. No difference between drugs in class.	Postural hypotension; dry cough; ↑K ⁺ ; Caution with renal dysfunction. Rarely angio-oedema. Not to be used during pregnancy.
ARB (Angiotensin II Receptor Blocker)	Suppression of RAA system	Reduction in BP similar to ACEIs. No difference between drugs in class.	Similar to ACEIs but ↓ risk of cough and angio-oedema.
CCB (Calcium Channel Blocker)	Interference with movement of calcium ions through cell membranes	BP reduction similar to other drugs in this table. May be good for isolated systolic hypertension.	Facial flushing; headaches; ankle oedema; postural hypotension. Some cause ↓ HR.
DIURETICS (Thiazides & thiazide like)	Inhibition of reabsorption of Na ⁺ at renal tubule level	Low dosage has shown BP ↓ similar to other drugs in table.	↓ K; ↑ risk of gout; ↑ risk of diabetes mellitus; rarely ↓ Na ⁺ .

The **dihydropyridine-type CCBs** (including amlodipine, lercanidipine and felodipine) reduce BP by relaxing the vascular smooth muscle cells and dilating coronary and peripheral arteries.¹³ The **“rate-limiting” CCBs** (including diltiazem and verapamil) affect the myocardial cells, reducing cardiac output and slowing heart rate, in addition to lowering BP. Studies have shown that low dose **thiazide-type diuretics** (including bendroflumethiazide, hydrochlorothiazide, chlorthalidone and indapamide) produce maximal or near maximal effect on BP reduction with no added benefit reported at higher dose levels.²⁴ Diuretics, such as spironolactone, which act as **aldosterone antagonists** have a role as add-on therapy in resistant hypertension.⁶ Care must be taken to monitor potassium as they can induce hyperkalaemia, especially in the presence of renal dysfunction.²⁶

Other Agents: For many years, **β-blockers** were used in the initial management of hypertension. However, there is conflicting evidence about their role in hypertension when used as monotherapy.^{20,27-8} Therefore, current guidelines recommend restricted use (see below). ADRs include bradycardia, bronchospasm, fatigue and cold extremities.¹³ **Alpha receptor blockers** (such as doxazosin) act at the alpha 1 receptor to cause vasodilatation. They may be considered as add-on therapy in resistant hypertension.^{12,29} ADRs include postural hypotension, headache, flushing and ankle oedema.²⁹

HYPERTENSION IN CLINICAL PRACTICE

Several reviews have evaluated the relative effectiveness of the drug classes listed in table 3, in terms of their protective effect against CV disease. There are methodological problems with some assessments because the level of BP reduction may not have been similar between studies and it has been shown that the larger the reduction in BP, the larger the reduction in CV risk.²⁵ In addition, the evidence base is less robust for some newer agents (e.g. ARBs) compared with older drugs.^{19,24} Moreover, it should be remembered that the majority of patients will require treatment with more than one agent to achieve optimal BP control. However, analyses have shown similar reductions in overall CV risk with the various drugs from these individual drug classes.⁵ **Whenever SBP is reduced by 10mmHg, irrespective of which agent is used from these classes, both stroke and coronary events are greatly reduced.**^{5,25} CCBs appear to confer greater protection against stroke but may be less effective than the other agents in the prevention of new onset heart failure;²⁸ low dose thiazides have been shown to be particularly effective in patients aged >80 years and in black populations, while ACEIs and ARBs appear to confer greater protection against coronary events.^{5,25,28}

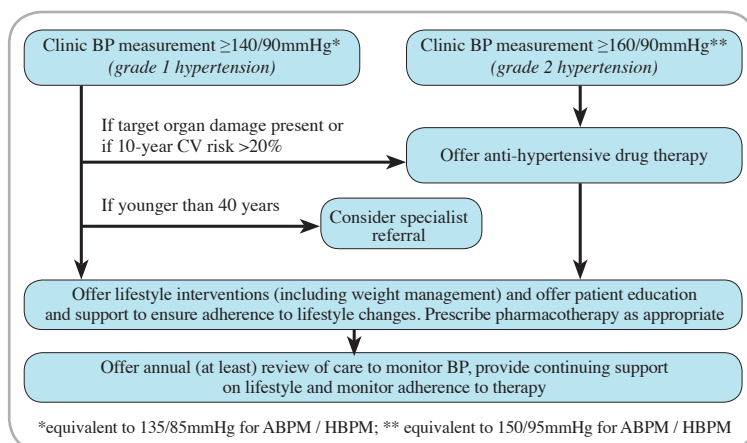
There are no clinical outcome data available on the efficacy of the various drug classes for the **younger age groups**, therefore some experts have used BP response as a surrogate marker.⁶ The results suggested that ACEIs (and β-blockers) are more effective at lowering BP in younger age groups compared with CCBs and diuretics, while initial treatment with CCBs or thiazides have been shown to be more effective at lowering BP in older people compared with ACEIs, ARBs, or β-blockers.

Combination Therapy: The majority of patients with hypertension will require the use of ≥2 drugs to achieve optimal control. Studies have reported maximal benefit from combining two drugs with different and complementary mechanisms of action.¹⁵ Comparison between a combination of an ACEI or ARB (A) plus CCB (C) and a combination of A plus low-dose thiazide (D) shows no significant differences in terms of overall mortality and CVS morbidity between the groups; the A+C combination has shown less study drug withdrawals and may be associated with an apparent increased benefit in reducing coronary events.⁶ It is estimated that **in up to 20% of patients hypertension is not controlled** with dual therapy;^{15,28} in these cases, an agent from the third class (either C or D) should be added.

Studies have shown no benefit in terms of CV outcome with **concomitant use of ACEI+ARB** and this combination is not routinely recommended in clinical practice.^{15,30} β-blockers may be considered as an option for use as combination therapy, especially in patients with existing CV disease (such as angina pectoris, stable heart failure, and prior myocardial infarct) or in those intolerant of other therapeutic options.¹² They should not be combined with diuretics in patients with existing metabolic syndrome or diabetes mellitus because of their combined dysmetabolic effects, and they should not be combined with a rate-limiting CCB because of the risk of heart block.^{13,15}

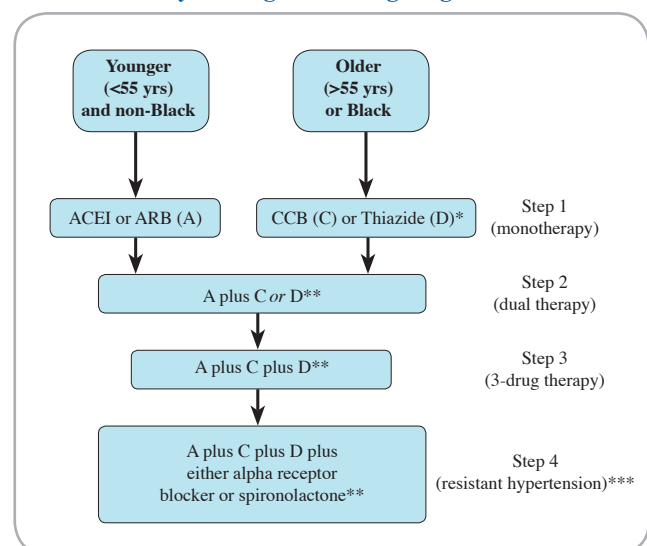
Figures 1 and 2 summarise the management of hypertension in practice, based on current guidance from the British Hypertension Society and NICE.^{6,12,31}

Figure 1:
Recommended Care Pathway for Hypertension: Summary¹²



All patients should be given education on weight management and lifestyle choices on an ongoing basis. In addition, each patient must have his/her CV risk estimated and be evaluated for evidence of target organ damage as these factors, in association with the BP level, will influence the management pathway, in particular with respect to the initiation of pharmacotherapy.

Figure 2:
Recommended Anti-Hypertensive Treatment: Summary^{6,12}
All patients should be offered ongoing education in relation to lifestyle changes including weight control



* CCB preferred unless patient has oedema, evidence of heart failure or has a high risk of heart failure or CCB not tolerated
 ** β-blocker may be considered as an alternative on a case-by-case basis;
 *** specialist referral should be sought

PRACTICAL ISSUES IN THE MANAGEMENT OF HYPERTENSION

The Elderly: BP increases with age, therefore hypertension (especially isolated systolic hypertension) is frequently diagnosed in older persons. In addition, increased SBP is a stronger risk factor for CV morbidity and mortality in older persons than increased DBP.³² Clinical studies have confirmed the beneficial effects of anti-hypertensive treatment in terms of all cause mortality, CV mortality and CV morbidity in those aged 60-80+ years.^{32,33} Elderly patients should be managed as outlined in figures 1 and 2; **the choice of anti-hypertensive agent will need to take account of existing medical conditions and concomitant medications.**³⁴ Since elderly patients may be particularly susceptible to postural hypotension and falls, (especially in the first weeks of treatment), dosages should be titrated slowly.³⁵ For those aged >80 years optimal control is defined as BP <150/90mmHg. **In the case of failure of therapy, problems with compliance should be ruled out before increasing dosage or adding in another medication.** Lifestyle advice will also improve BP control and reduce overall CV risk.³⁴

Diabetes Mellitus is a major risk factor for CV disease therefore hypertension must be actively managed by both pharmacotherapy and lifestyle interventions.³⁶ Management should aim to achieve a BP of <130/80mmHg and depending on the individual patient, consideration should be given to starting pharmacotherapy for high normal BP levels, (e.g. when microalbuminuria is detected).^{5,36} Since ACEIs / ARBs have renoprotective effects, these are the drugs of first choice.³⁶ Diabetic patients with hypertension should also receive standard CV disease preventive therapies.¹²

Management of hypertension during pregnancy aims to (1) protect the mother from CV complications and (2) protect the foetus from adverse effects of treatment. This topic was covered in a previous bulletin (<http://www.stjames.ie/GPsHealthcareProfessionals/Newsletters/NMICBulletins/NMICBulletins2006/>).³⁷ The possibility of pregnancy should always be taken into account when deciding on anti-hypertensive therapy for **women of child-bearing potential.**

Maintenance of Optimal Anti-hypertensive Therapy: Generally, once hypertension is diagnosed, anti-hypertensive therapy should be maintained indefinitely.¹⁴ Although there is a strong evidence-base for the benefits of appropriate management of hypertension, less than half of hypertensive patients achieve BP goals, even with active treatment, a situation which has remained unchanged over the last 30 years.³⁸ Extensive clinical data on best ways of optimising BP control are lacking, **however studies have shown that an organised system of regular review of patients in the clinic, together with a dedicated implementation of the pharmacotherapy stepped-care approach (see figure 2) results in the best BP control and CV outcome.**³⁸ Initiatives such as self-monitoring, appointment reminders and pharmacist involvement also appear to be associated with improved BP control.^{38,39} More research is needed in this area in order to identify how to achieve and maintain optimal BP control and maximise patient benefit.

SUMMARY

Hypertension is a major cause of CV mortality and morbidity. Once diagnosed, management needs to take into account, not only the level of elevated BP, but also the degree of CV risk and the presence or absence of target organ damage. All patients should receive education and ongoing support in relation to improving dietary habits and increasing physical activity and they should be encouraged to stop smoking. When pharmacotherapy is indicated, a stepped care approach is recommended. It is important to remember that the majority of patients will require dual therapy and up to 20% will need triple therapy in order to achieve optimal BP control, therefore patients should be monitored regularly and progressed along the treatment steps in order to achieve optimal control. Once the patient is controlled (BP <140/90mmHg or <150/90mmHg for those aged >80 years) regular review is recommended to ensure maintenance of BP control and to reinforce the education on weight control and a healthy lifestyle.

Table 4 outlines the top ten anti-hypertensive agents prescribed in Ireland during 2010 and provides details on the relative costs of these agents.

Table 4: “Top Ten” single anti-hypertensive agents* prescribed in Ireland⁴⁰⁻⁴⁸

Name	Drug Class	Recommended Dosage**	Total ingredient cost €	Generic available (Nov 2011)
Amlodipine	CCB	5-10mg/day	7,276,573	yes
Ramipril	ACEI	2.5-10mg/day	5,296,541	yes
Perindopril	ACEI	5-10mg/day	7,655,298	yes
Bendroflumethiazide (with K+)	Thiazide	2.5-5mg/day	777,885	no
Lercanidipine	CCB	10-20mg/day	2,989,394	yes
Bendroflumethiazide	Thiazide	2.5-5mg/day	380,153	***
Lisinopril	ACEI	10-20mg/day	1,648,126	yes
Valsartan	ARB	80-320mg/day	4,810,236	****
Losartan	ARB	50-100mg/day	3,887,410	yes
Telmisartan	ARB	40-80mg/day	3,094,370	no

*based on data from the Primary Care Reimbursement Scheme, January – December 2010

** under normal conditions as per the Summary of Product Characteristics for each medicine; dose regimen may need to be altered on a case-by-case basis;

no longer licensed as a single agent in Ireland; *generic versions available from December 2011

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List of references available on request. Date of preparation: November 2011

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 individual Summary of Product Characteristics (SmPC) for specific information on a drug.

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