National Medicines Information Centre
ST. JAMES'S HOSPITAL • DUBLIN 8
TEL 01-4730589 or 1850-727-727 • www.nmic.ie
VOLUME 24
NUMBER 6
2018

UPDATE ON MANAGEMENT OF HYPERTENSION

- **Hypertension is defined as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg**
- **Hypertension is one of the most important preventable causes of premature morbidity and mortality**
- **Unidentified and uncontrolled hypertension is a global health issue**
- **Combination pharmacological therapy is required in most patients to control hypertension**

INTRODUCTION

There has been a global decrease in mortality from cardiovascular disease (CVD) over the last 20 years, however CVD remains a leading cause of death worldwide.[1,2] **Hypertension is a major risk factor for stroke, myocardial infarction (MI), heart failure, chronic kidney disease (CKD) and cognitive decline and is one of the most important preventable causes of premature morbidity and mortality.**[1,3-7] Figures from 2015 estimate that hypertension was responsible for approximately 10 million deaths globally and > 200 million disability-adjusted life years.[8] The overall prevalence of hypertension, which is expected to increase, is approximately 30 to 45%.[9] **Hypertension becomes more common with advancing age;**[3,4] the Irish Longitudinal Study on Ageing (TILDA), involving prospective follow-up of participants ≥50 years reported a prevalence of hypertension of 64% in 2015.[1]
The risk associated with increasing blood pressure (BP) is continuous, with each 2 mmHg rise in systolic BP (SBP) associated with a 7% increased risk of mortality from ischaemic heart disease and a 10% increased risk of mortality from stroke.[3,4] Studies have shown that a 10 mmHg reduction in SBP or a 5 mmHg reduction in diastolic BP (DBP) is associated with significant reductions in all major CV events by 20%, all-cause mortality by 10 to 15%, stroke by 35%, coronary events by 20% and heart failure by 40%.[10-13] **Unidentified and uncontrolled hypertension is a major global public health issue;**[3,5,14] evidence from a multinational study reported that 46.5% of people were unaware that they had hypertension and BP was only controlled in 32.5% of treated patients.[9] In an Irish context, the TILDA study found that 55% of hypertensive patients were aware that they had hypertension and 59% were on anti-hypertensive medication, of which 52% had their BP controlled to <140/90 mmHg.[1]
The European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) have recently published updated guidelines on the management of hypertension.[3]
This bulletin will outline the current management of hypertension.

DIAGNOSIS OF HYPERTENSION

Classification: Hypertension is defined as an office SBP of ≥140 mmHg and/or a DBP of ≥90 mmHg; BP is classified as optimal, normal, high-normal, and grades of 1 to 3 hypertension, according to clinic BP (table 1).[3] As **hypertension is an asymptomatic condition and many people are unaware that they have hypertension, opportunistic screening of adults is advised,** with further screening undertaken at regular intervals.[3]

Table 1: Classification and screening of blood pressure in adults[3*]

Category	Systolic (mmHg)		Diastolic (mmHg)	Screening interval
Optimal	<120	and	<80	Every 5 years
Normal	120 – 129	and/or	80 – 84	Every 3 years
High-normal	130 – 139	and/or	85 – 89	Every year
Grade 1 hypertension	140 – 159	and/or	90 – 99	N/A
Grade 2 hypertension	160 – 179	and/or	100 – 109	N/A
Grade 3 hypertension	≥180	and/or	≥110	N/A
Isolated systolic hypertension	≥140	and	<90	N/A

*based on the 2018 European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) guidelines

Blood pressure measurement is often performed improperly; BP devices need to be validated and regularly recalibrated.[3,4] The patient's BP should be measured while seated, with the arm outstretched and supported, initially in both upper arms, with an appropriate cuff size.[3,4] The arm with the higher BP values should be used for future measurements.[3,4] Three BP measurements (1 to 2 minutes apart) should be taken and the BP recorded as an average of the last two BP measurements; additional measurements are needed if the readings differ by >10 mmHg.[3] **In older people, those with diabetes or other risk factors for orthostatic hypotension** (which is associated with an increased risk of mortality and CV events), BP should be measured 1 and 3 min after standing.[3]
If clinic BP is ≥140/90 mmHg, the patient should be offered out of office BP measurement, either ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM).[3,4] ABPM provides the average of BP readings usually over 24 hours and is often lower than clinic BP; **the diagnostic threshold for hypertension using ABPM is ≥130/80 mmHg over 24 hours,** ≥135/85 mmHg for the daytime average and ≥120/70 mmHg for the night-time average.[3] HBPM is the average of all BP readings (performed with a validated BP monitor), from at least 3 days (preferably from 7 consecutive days); readings should be taken in the morning and evening in a quiet room after 5 min of rest.[3,4] Two measurements should be taken at each measurement session, performed 1 to 2 min apart.[3] **The diagnostic threshold for hypertension using HBPM is ≥135/85mmHg.**[3]
ABPM and HBPM are useful in the diagnosis of **white coat hypertension,** and may also be useful to exclude **masked hypertension.**[3] Masked hypertension occurs in approximately 15% of patients with high-normal clinic BP; it is associated with an increased risk of CV events. It has a greater prevalence in younger people, men, those who smoke, have higher levels of physical activity, alcohol consumption, anxiety and job stress.[3]

Diagnosis: The diagnosis of hypertension should be based on repeated clinic BP measurements or out-of-office BP measurements with ABPM and/or HBPM.[3] However, if the patient's SBP is ≥180 mmHg and/or DBP is ≥110 mmHg, consider starting antihypertensive drug therapy immediately without waiting for the results of ABPM or HBPM.[4] Table 2 outlines factors that should be considered in the assessment of a patient with hypertension. **Secondary causes of hypertension occurring in 5 to 15% of people with hypertension should be considered** (see Table 2).[3] The diagnosis of hypertension should include assessment for **the presence of target organ damage (TOD)** (also known as hypertensive-mediated organ damage), such as left ventricular hypertrophy, CKD, or retinopathy.

Table 2: Factors to be considered in an assessment of a patient with hypertension[3]

Medical history to include assessment of:	Key steps in physical examination include:
Risk factors • Patient or F/H of hypertension, CVD, stroke or renal disease, hypercholesterolaemia • Smoking history • Dietary history and alcohol consumption • Previous hypertension in pregnancy/pre-eclampsia **History of possible secondary hypertension including** • Young onset of grade 2 or 3 hypertension (<40 years), or sudden development of hypertension or rapidly worsening BP in older patients • History of renal/urinary disease • Concurrent therapies/recreational drug/substance abuse e.g. corticosteroids, oral contraceptives, nasal decongestants, stimulants, liquorice, NSAIDs • Repetitive episodes of sweating, headache, anxiety or palpitations suggestive of phaeochromocytoma • History of spontaneous or diuretic-provoked hypokalaemia, episodes of muscle weakness and tetany (hyperaldosteronism) • Symptoms suggestive of thyroid disease or hyperparathyroidism **Antihypertensive Therapy** • Current/past antihypertensive medication including effectiveness and intolerance to previous medications • Adherence to therapy	**Body habitus** • Weight and height with calculation of BMI • Waist circumference **Assess for signs of target organ damage** • Neurological examination and cognitive status • Fundoscopic examination for hypertensive retinopathy • Palpation and auscultation of heart and carotid arteries • Palpation of peripheral arteries • Comparison of BP in both arms (at least once) **Assess for secondary hypertension including:** • Auscultation of heart and renal arteries for murmurs or bruits indicative of aortic coarctation or renovascular hypertension • Comparison of radial with femoral pulse: to detect radio-femoral delay in aortic coarctation • Signs of Cushing's disease or acromegaly • Signs of thyroid disease **Routine baseline laboratory tests include:** • Haemoglobin, fasting blood glucose and glycated HbA1c, blood lipids (total cholesterol, LDL and HDL cholesterol), triglycerides, potassium, sodium, uric acid, creatinine (and eGFR), liver function tests • Urine analysis: microscopic; urinary protein by dipstick or ideally albumin:creatinine ratio • 12-lead ECG

F/H-family history; CVD-cardiovascular disease; NSAIDs-non-steroidal anti-inflammatory drugs

Cardiovascular risk assessment: Formal CV risk assessment is recommended using a validated risk assessment tool such as Systematic COronary Risk Evaluation (SCORE).[3] SCORE estimates the 10 year risk of fatal CVD in relation to 1) age, 2) gender, 3) smoking habits, 4) total cholesterol and 5) SBP.[2,3] HeartScore is an electronic CVD risk assessment tool, which is similar to SCORE and includes HDL as a 6th variable;[2] it is available on **www.heartscore.org**. Hypertensive patients with documented CVD, diabetes mellitus (DM) type 1 or 2, CKD and very high levels of individual risk factors (including grade 3 hypertension) are automatically considered to be at very high (i.e. ≥10% CVD mortality) or high (i.e. 5-10% CVD mortality) 10 year CV risk, and do not need formal CV risk estimation to determine the need for treatment of their hypertension.[3]

MANAGEMENT

There is a large body of evidence to show that lowering BP in hypertensive patients results in reduced CV outcomes and death,[6,7,15-21] including in patients >65 years.[22-26] **Current guidelines recommend that patients with grade 2 or 3 hypertension and patients with grade 1 hypertension with high CV risk or TOD should be treated with BP lowering drugs and lifestyle intervention.**[3,4,27] Recent evidence suggests that treatment of patients with grade 1 hypertension at low to moderate CV risk is likely to reduce mortality,[6,7,15-17] and evidence also supports BP lowering treatment of older patients (>65 years and >80 years).[22-26] Evidence does not support the use of BP lowering treatment for patients with high-normal BP, although it may be considered in these patients with established CVD.[3] Table 3 summarises the 2018 ESC/ESH guidelines for treatment thresholds.

Table 3: Initiation of hypertension treatment according to clinic blood pressure[3]

Treatment threshold	Recommendation
Grade 1 hypertension	
• Patients at low to moderate risk and no evidence of TOD	BP lowering treatment if patient remains hypertensive after period of lifestyle changes
• Patients at high CV risk or TOD	Prompt initiation of drug treatment simultaneously with lifestyle changes
Grade 2 or 3 hypertension at any level of CV risk	Prompt BP lowering treatment simultaneous with lifestyle changes
Older patients	
• Fit patients (including >80 years) when SBP ≥160 mmHg	BP lowering treatment and lifestyle changes
• Fit patients (>65 years but not >80 years) when SBP is grade 1 (140-159 mmHg)	BP lowering treatment and lifestyle changes, provided that treatment is well tolerated
High-normal BP (130-139/85-89 mmHg)	Lifestyle changes; drug treatment may be considered when CV risk is very high due to established CVD, especially CAD

TOD-target organ damage; BP-blood pressure; CVD-cardiovascular disease; CAD-coronary artery disease; SBP-systolic blood pressure

Non-pharmacological management

Lifestyle changes are recommended for all patients with hypertension.[3] Lifestyle measures to reduce BP include 1) salt restriction (<5 g/per day), 2) moderation of alcohol intake (<14 units/week for men and <8 units/week for women), 3) high consumption of vegetables/fruits and low consumption of red meat, 4) weight reduction and 5) physical activity (at least 30 minutes of moderate exercise on 5 to 7 days per week).[3,28-31] Diets such as the Mediterranean and the

Dietary Approaches to Stop Hypertension (DASH) are associated with improved CV outcomes.[32-34] Advice on smoking cessation is also recommended.[3,28-31] Patient education is important, as a lack of awareness is associated with poor medication adherence.[35]

Pharmacological management

There are five major drug classes which are recommended for the treatment of hypertension: angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), which inhibit the renin-angiotensin-aldosterone system (RAAS), calcium channel blockers (CCBs), thiazides and thiazide-like diuretics and beta-blockers.[3] These drug classes have similar effectiveness in reducing BP and reducing major CV outcomes and mortality.[3] Beta blockers are effective at lowering BP and reducing CV morbidities,[13] however they are not as effective in preventing stroke and mortality compared to other anti-hypertensive agents.[3,36-38] **Beta blockers may be useful in specific situations** e.g. coronary artery disease, heart failure, angina, atrial fibrillation, post-MI and as an alternative to RAAS blockers in young hypertensive women of child bearing potential and in pregnancy.[3] Table 4 summarises the four most frequently prescribed anti-hypertensive therapies. Treatment needs to be individualised to the patient as contraindications/ precautions exist for each class of drug. **For most patients with hypertension, combination pharmacological agents are required to achieve BP control** (discussed below).[3,35] The Summary of Product Characteristics should be referred to for full prescribing details.

Table 4: The four most frequently prescribed anti-hypertensive therapies[3,13,39-48]

Drug class	Comments	Contra-indications /precautions include*	Adverse effects include*
Angiotensin Converting Enzyme Inhibitor (ACEI) • e.g. Ramipril**	Reduce albuminuria more than other BP lowering drugs. Effective at delaying the progression of diabetic and non-diabetic CKD. Also indicated post MI and in HF which are frequent complications of hypertension. ↓efficacy in people of black African origin as monotherapy but not as combination.	Not recommended in pregnancy and C/I in second and third trimesters of pregnancy. C/I in severe hepatic impairment and/or cholestasis. C/I in bilateral renal artery stenosis. K+ monitoring required in patients with renal impairment and those on K+ supplements or K+ sparing drugs. Not recommended to use combinations of ACEI and ARB as it ↑ risk of adverse renal effects. **(Use only under specialist supervision and not in diabetic nephropathy).**	Postural hypotension, ↑K+; GI effects; rash; myalgia; dry cough with ACEI; ↑ risk of angioedema with ACEI, especially in people of black African origin (ARB may be preferred)
Angiotensin II Receptor Blocker (ARB) • e.g. Candesartan**			
Calcium Channel Blocker (CCB) • Dihydropyridines e.g. amlodipine** • Non-dihydropyridines e.g. diltiazem, verapamil	May be less effective in preventing HF than other therapies. Dihydropyridines are preferred to non-dihydropyridines.	C/I in unstable HF; use with caution in HF. Non-dihydropyridines – C/I in HF, sick sinus syndrome, 2nd or 3rd degree heart block. Avoid with beta blockers.	Facial flushing; headaches; oedema; postural hypotension; palpitations; GI effects. Non-dihydropyridines also associated with bradycardia.
Diuretics • Thiazides e.g. bendroflumethiazide, hydrochlorothiazide • Thiazide-like diuretics e.g. chlorthalidone, indapamide	May be more effective than other therapies in preventing HF. Thiazide and thiazide-like have similar efficacy.	C/I in AD; hypercalcaemia; hyponatraemia; refractory hypokalaemia; symptomatic hyperuricaemia. Monitor K+; reduce dose in the elderly; may exacerbate diabetes and gout.	Headache; ↓K+; constipation; postural hypotension. ↑risk of non-melanoma skin cancer with HCTZ.

*-full prescribing information is available in the Summary of Product Characteristics; **-current preferred drug by the HSE Medicines Management Programme
HF-heart failure; CKD-chronic kidney disease; BP-blood pressure; MI-myocardial infarction; K+-potassium; GI-gastrointestinal; AD-Addison's disease; HCTZ-hydrochlorothiazide

Other anti-hypertensive drugs: Spironolactone, additional diuretic therapy and alpha blockers are not recommended for the routine treatment of hypertension however they may be used as add-on therapy for patients with resistant hypertension.[3]

Practical aspects of hypertension management

Two-drug therapy: The majority of people will require combination pharmacological therapy to control their hypertension. **Studies have shown that two-drug combination therapy will control BP in approximately two-thirds of people;** recent guidelines recommend the use of two agents (preferably in a fixed dose combination) in the initial pharmacological management of hypertension (see figure 1).[3,35] A combination of an ACEI or ARB with a CCB or thiazide/thiazide-like diuretic is preferred as their actions are complementary (CCBs or diuretics activate the RAAS which is balanced by their combination with an ACEI or ARB); this reduces the potential for adverse effects.[3,35] Combinations of a CCB and diuretic although effective, are not the preferred first choice combination as there is less evidence to support their use and they do not inhibit the RAAS which may be desirable in some patients;[3,35] this combination may have a role if a RAAS inhibitor is not well tolerated and/or contraindicated, such as in pregnancy.[35] The increased risk of non-melanoma skin cancer associated with hydrochlorothiazide,[48] merits consideration when selecting combination therapy. **Combination therapy of ACEI and ARBs should be avoided as it is associated with impaired renal outcomes.**[49]

Three-drug therapy: Patients not controlled on two-drug therapy, should be increased to treatment with three-drug combination therapy, usually **a RAAS blocker, CCB and a diuretic, which should control BP in >80% of patients.**[3] Beta blocker containing drug combinations may be used if there is a specific indication for their use.[3,38] Caution should be used with a beta blocker/diuretic combination, which is associated with increased risk of glucose intolerance and DM.[35,50] The current ESC/ESH treatment algorithm is outlined in figure 1.

Figure 1: Treatment strategy for uncomplicated hypertension[3]

One pill	**Initial therapy** Two-drug combination	**ACEI or ARB + CCB or diuretic**	Consider monotherapy* in low risk grade 1 hypertension (systolic BP <150mmHg) or in very old (≥80 years) or more frail patients
One pill	**Step 2** Three-drug combination	**ACEI or ARB + CCB + diuretic**	
Two pills	**Step 3** Three-drug combination + spironolactone or other drug	**Resistant hypertension** Add spironolactone or other diuretic, beta blocker or alpha blocker	Consider referral to a specialist centre for further investigation
	Beta blockers Consider beta-blockers at any treatment step, when there is a specific indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation, or younger women with, or planning pregnancy		

ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; CCB – calcium channel blocker; MI – myocardial infarction; *-consider monotherapy for patients with high-normal BP and established CVD

Resistant hypertension: Patients whose BP remains uncontrolled on three-drug combinations should be classified as having resistant hypertension, which occurs in <10% of treated patients.[3] Patients with resistant hypertension are at a higher risk of TOD, CKD and CV events. **Secondary causes of hypertension and poor adherence should be excluded in these patients.**[3,51]

The elderly: Studies have confirmed the beneficial effects of antihypertensive treatment in those aged >65 years (including those aged >80 years).[22-26] It is recommended that older patients are treated according to the treatment algorithm in figure 1 however **the treatment decision must take into account the patient's clinical condition, concomitant medications and frailty.**[3] Combination therapy when used, should be started at the lowest available dose, and monotherapy should be considered for those aged >80 years.[3] **In all older patients, monitoring for postural hypotension is required.**[3]

Referral for specialist advice may be required for patients where 1) secondary hypertension is suspected, 2) younger patients (<40 years) with grade 2 or more severe hypertension, 3) patients with treatment-resistant hypertension, 4) patients who require assessment of TOD, 5) patients with sudden onset of hypertension when BP has previously been normal and 6) other clinical circumstances in which the referring doctor feels more specialist evaluation is required.[3]

Blood pressure targets: It is recommended that when BP lowering drugs are used the first objective should be to lower BP to <140/90 mmHg in all patients.[3] If treatment is well tolerated, a target BP as shown in table 5 is recommended.[3,16,52]

Table 5: Clinic blood pressure treatment target range[3]

Age range	Clinic SBP treatment target ranges (mmHg)					Clinic DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ Chronic kidney disease	+ CAD	+ Stroke*/TIA	
18-65 years	Target to ≤130 if tolerated Not <120**	Target to ≤130 if tolerated Not <120**	Target to <140 and to 130 if tolerated	Target to ≤130 if tolerated Not <120**	Target to ≤130 if tolerated Not <120**	70-79
65-79 years* **	Target to 130-139 if tolerated	Target to 130-139 if tolerated	Target to 130-139 if tolerated	Target to 130-139 if tolerated	Target to 130-139 if tolerated	70-79
≥80 years* **	Target to 130-139 if tolerated	Target to 130-139 if tolerated	Target to 130-139 if tolerated	Target to 130-139 if tolerated	Target to 130-139 if tolerated	70-79
Clinic DBP target range (mmHg)	70-79	70-79	70-79	70-79	70-79	

SBP-systolic blood pressure; DBP-diastolic blood pressure; CAD-coronary artery disease; TIA-transient ischaemic attack
***refers to patients with previous stroke and does not refer to BP targets immediately after stroke; **treated SBP should not be targeted to <120mmHg; ***treatment decisions and BP targets may need to be modified in frail older patients**

Uncontrolled hypertension: Reasons for poor control of hypertension include poor adherence to treatment (<50%) and therapeutic inertia (i.e. failure to adequately uptitrate treatment).[3,14] Methods to improve adherence include patient education and self-managed BP monitoring (e.g. HBPM).[3,5] **Adherence to treatment has also been shown to be negatively impacted by complexity of treatment regimens**; non-adherence is <10% with one pill, rising to 20% with 2 pills, 40% with 3 pills and very high rates of partial or complete non-adherence in patients on ≥5 pills.[53] **The use of fixed dose combinations of drugs has been shown to be associated with improved adherence and can lead to a lower risk of CV events.**[35,53,54] Therapeutic inertia is also thought to contribute to suboptimal BP control with many patients remaining on monotherapy and/or suboptimal doses despite inadequate BP control.[3,35]

SUMMARY

Hypertension is one of the most important preventable causes of premature morbidity and mortality, however, unidentified and uncontrolled hypertension is a major global health issue. The most effective treatment strategy to improve BP control is 1) lifestyle interventions for all patients, 2) a treatment algorithm that applies to all patients and is pragmatic, with the use of combination (preferably fixed dose combination) as initial therapy for most patients with some exceptions (low risk patients with stage 1 hypertension, very high risk patients with high-normal BP range and in frail older patients).

List of references available on request. Date of preparation: Jan 2019

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