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Essential hypertension

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Management approach

The main goal of treatment is to decrease the risk of mortality and of cardiovascular and renal morbidity. [5] The following recommendations are based on the eighth Joint National Committee (JNC 8) guidelines. JNC 8 states that BP goal should be <140/90 mmHg for adults aged 18-59 years, including those with diabetes or chronic kidney disease, and <150/90 mmHg in the general population beginning at age 60 years. [4]

In the general population aged ≥60 years, the eighth Joint National Committee (JNC 8) guideline recommends pharmacological therapy to lower blood pressure when BP ≥150/90 mmHg. [4] However, some panel members recommended retaining the JNC 7 systolic BP goal of <140 mmHg, concluding that there was insufficient evidence to implement the less intensive target in high-risk groups, including black people, those with cardiovascular disease, and those with multiple risk factors. [60]

Evolving treatment goals

Blood pressure goals are evolving as more studies are being carried out. [61] The SPRINT trial (Systolic Blood Pressure Intervention Trial) ended early as it found that a lower systolic target of 120 mmHg (as measured by automated office blood pressure [AOBP]) reduced cardiovascular complications and deaths in people aged over 50 years with high blood pressure and at least one additional risk factor for heart disease. [62] [63] Patients with diabetes or stroke were excluded from the trial. However, in the HOPE-3 trial, intermediate-risk people without cardiovascular disease did not benefit from BP lowering unless in the highest tertile of starting BP (as opposed to higher-risk patients in SPRINT). [64]

Because of differences in the general health of older patients, the decision to treat should be on an individual basis, and BP lowering should be gradual and carefully monitored by the physician. [2] [65] The SPRINT trial results showed equal benefit in people aged >75 years, regardless of frailty or walking speed. [66] However, one systematic review found insufficient evidence regarding the benefits of hypertension treatment for frail people >80 years of age taking multiple medications, concluding that treatment should be individualised. [67]

Regarding patients with concomitant diabetes mellitus, there is good-quality evidence that very intensive BP lowering (targeting a systolic pressure <120 mmHg, as compared with

targeting <140 mmHg) does not lessen risk (composite outcome: non-fatal MI, non-fatal stroke, or death from cardiovascular cause) and may increase risk of adverse events. [11]

Lifestyle modification

The initial approach to a newly diagnosed patient should include a thorough explanation of the risks associated with HTN and the need for adequate control and adherence to therapy. Initial therapeutic measure should be lifelong lifestyle modification including: [3] [12] [44] [68] [69] [70]

- Sodium reduction (≤2.4 g/day)
- Dietary Approaches to Stop Hypertension (DASH) diet (8-10 servings of fruit and vegetables daily, whole grains, low sodium, low-fat proteins)
- Waist circumference <102 cm for men and <88 cm for women; weight loss to a BMI of about 25 kg/m^2
- Increased physical activity: at least 30 minutes of moderate-intensity dynamic aerobic exercise (walking, jogging, cycling, or swimming) 5 days per week to total 150 minutes per week, as tolerated or recommended by physician
- Limited alcohol consumption: less than 2-3 standard drinks (<20-30 g alcohol) per day in hypertensive men; less than 1-2 standard drinks (<10-20 g alcohol) per day in hypertensive women. Total weekly alcohol consumption should not exceed 14 standard drinks (140 g) for men and 8 standard drinks (80 g) for women.

Advice about lifestyle modification should be given upon diagnosis and should continue concurrently with all other therapeutic measures. Prior to initiation of an exercise programme, patients should discuss a plan with their healthcare provider.

Smoking cessation should always be encouraged as well, to promote general vascular health, though smoking cessation has not been associated with decreased BP.

A 3-month trial is recommended in adherent patients willing to make therapeutic lifestyle changes, prior to determining that pharmacological therapy is necessary. Most patients will require drug therapy to achieve target BP control.

Antihypertensive drugs

Examples of the main classes of antihypertensives that were recommended by JNC 8 include: [4]

- Diuretics:
  - Thiazide (or thiazide-like): hydrochlorothiazide, chlortalidone, indapamide
- ACE inhibitors: lisinopril, enalapril, captopril
- Angiotensin-II receptor antagonists: candesartan, irbesartan, losartan, valsartan
- Calcium-channel blockers: amlodipine, diltiazem
- Beta-blockers: metoprolol, atenolol

Some of these drugs are available in fixed-dose combination formulations. These single pill formulations simplify dosing regimens and improve adherence. [71]

Drug therapy for stage 1

For stage 1 HTN (BP 140 to 159/90 to 99 mmHg) monotherapy can be initiated or combination therapy considered. Evidence does not favour one approach. [3] [Cochrane] The choice of antihypertensive agent is driven by efficacy, adverse-effect profile, and cost. Many people with stage 1 HTN have a constellation of other cardiovascular risk factors such as smoking or mild dyslipidaemia that increase the importance of BP lowering.

If BP cannot be controlled with a single agent, a drug from a different class of antihypertensives is added.

Generally, when an ACE inhibitor would usually be chosen but is not tolerated, an angiotensin-II receptor antagonist can be substituted.

Stage 1 HTN: without CVD-related comorbidity or chronic renal disease, or with diabetes

A choice among four preferred classes of drugs is recommended for initial therapy. [4] [72]

Thiazide (or thiazide-like) diuretics have been shown to be safe and efficacious first-line therapy. They also decrease renal calcium excretion, so may be a good choice for women with osteoporosis. As with all antihypertensive medications, the initial dose should be the lowest possible, and then titrated for a therapeutic effect, while observing for potential adverse effects.

Alternative first-line choices include ACE inhibitors, angiotensin-II receptor antagonists, or calcium-channel blockers, or a combination of two different drugs from these classes (excluding the combination of ACE inhibitors and angiotensin-II receptor antagonists). Aliskiren, a direct renin inhibitor, is also available; however, its place in the treatment pathway is not yet clear due to concerns about risks in combination with ACE inhibitors or angiotensin-II receptor antagonists, and in the settings of diabetes or renal impairment; [62] and it it is not considered to be a preferred option.

In the general black population, including those with diabetes, the JNC 8 guideline recommends a thiazide (or thiazide-like) diuretic or a calcium-channel blocker as initial pharmacological therapy. [4] The recommendation is derived from a pre-specified subgroup analysis of black patients, 46% of whom had diabetes, in the ALLHAT trial. [73] [74]

In patients with diabetes who have increased albumin excretion, ACE inhibitors or angiotensin-II receptor antagonists are recommended. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study showed that chlortalidone, amlodipine, or lisinopril were co-equal for mild HTN in type 2 diabetes. [73] ACE inhibitors are renoprotective, decreasing the progression of proteinuria in diabetic patients. [75] Sleep-time BP is the most significant independent prognostic marker of cardiovascular events in diabetes.

Comorbid CAD

Beta-blockers are first-line. Beta-blockers have proven beneficial in patients with chronic stable angina, post-MI, or CHF, in patients with CAD undergoing surgery, or in patients with hypertrophic obstructive cardiomyopathy. [76] [77] [78] [79] [80]

Many patients with CAD also take nitrates, which act as an exogenous nitric oxide (NO) donor. Modest reductions in systolic BP can be observed, but the US Food and Drug Administration (FDA) has not approved the use of nitrates solely as antihypertensive therapy. [23]

ACE inhibitors have been shown in some trials to decrease cardiovascular events, while other studies have not demonstrated a benefit for ACE inhibitors in the setting of stable CAD with normal LV function. [81] [82] [83]

Comorbid CHF

In patients with comorbid CHF, an ACE inhibitor (or an angiotensin-II receptor antagonist if not tolerated) plus a beta-blocker with or without an aldosterone antagonist is used.

ACE inhibition has been shown to convey a survival advantage in patients with CHF. [77] [84] Angiotensin-II receptor antagonists also decrease morbidity and mortality. [85] [86] Compared with ACE inhibitors, angiotensin-II receptor antagonists were equivalent, but not superior, in the treatment of patients with CHF. [87] [88]

Beta-blockers have proven mortality benefits in patients with chronic CHF. [78] [79]

Aldosterone antagonists should be given to patients with heart failure and ejection fraction under 35% who are taking optimised ACE inhibitor or angiotensin-II receptor antagonist plus beta-blocker treatment, who still require antihypertensive therapy. Blockade of aldosterone has been associated with decreased end-organ fibrosis. [89]

Diuretics (non-aldosterone) confer no mortality benefit for patients with CHF. However, they are frequently used to relieve symptoms of fluid overload.

The combination of hydralazine and a nitrate (e.g., isosorbide dinitrate/hydralazine) has been shown to be of benefit for black patients already taking ACE inhibitors, beta-blockers, and aldosterone antagonists, as well as in all patients with CHF who are intolerant of both ACE inhibitors and angiotensin-II receptor antagonists. [90] [91]

Sacubitril/valsartan and ivabradine are newer drugs also used for chronic heart failure.

Comorbid LVH or renal disease

ACE inhibition has proven beneficial across a myriad of cardiovascular disease states including CHF and LVH. [81] [82] An ACE inhibitor is first choice for comorbid renal disease, and an angiotensin-II receptor antagonist is first choice for comorbid LVH.

Angiotensin-II receptor antagonists have been shown to decrease morbidity and mortality in patients with HTN and LVH. [85]

Comorbid atrial fibrillation (AF)

First choice is a beta-blocker. Second choice is a non-dihydropyridine calcium-channel blocker.

Evidence from post-hoc analyses suggest that angiotensin-II receptor antagonists and ACE inhibitors do not prevent the occurrence [92] [93] or the recurrence [94] [95] of atrial fibrillation. One meta-analysis found that telmisartan was more effective than other anti-hypertensive drugs in preventing AF recurrences among hypertensive patients with paroxysmal AF. [96] This could be related to a specific effect of telmisartan on atrial electric remodeling, but more investigation is needed.

Comorbid benign prostatic hypertrophy

The ALLHAT study conclusively demonstrated that alpha-blockers should not be a first-line antihypertensive therapy for patients with symptomatic benign prostatic hypertrophy (BPH). In these patients, the preferred first-line antihypertensive options are the same as for most other groups (i.e., thiazide [or thiazide-like] diuretics, ACE inhibitors, angiotensin-II receptor antagonists, and calcium-channel blockers), and the alpha-blocker indication is simply to treat the BPH symptoms.

Comorbid Raynaud's disease, PVD, or coronary artery spasm

Calcium-channel blockers are first choice. In addition to vascular disease, calcium-channel blockers are also useful for persistent angina or stroke prevention. [97] [98]

Stage 2 HTN

Patients presenting with stage 2 HTN (BP >160/100 mmHg) will probably require more than one drug for BP control. Therefore, the initiation of two concurrent antihypertensives is recommended.

The combination of a non-dihydropyridine calcium-channel blocker with a beta-blocker should be avoided, because of an increased risk of high-degree AV block.

Recalcitrant (resistant) HTN

Managing recalcitrant HTN requires expertise. Frequently requiring multiple antihypertensive agents, patients must be observed and counselled regarding adverse effects, medication adherence, potential drug-drug interactions, and metabolic abnormalities. Infrequently, patients will require a screen for secondary causes of HTN.

Representative agents of the main treatment class options, namely thiazide (or thiazide-like) diuretics, ACE inhibitors, angiotensin-II receptor antagonists, and calcium-channel blockers, should be maximised. ACE inhibitors and angiotensin-II receptor antagonists should not be used together due to the risk of acute renal failure.

The fourth-line drug option is generally spironolactone. Usual safety parameters for the use of spironolactone include:.

1. Presence of another diuretic already being taken
2. GFR >50 mL/min/1.73m2
3. Baseline potassium level <4.5 mmol/L (mEq/L).

Otherwise, a safe fourth- or fifth-line option is a peripheral adrenergic blocker. Hydralazine is a less-preferred option due its twice-daily dose requirement and increased risk of oedema with simultaneous calcium-channel blocker treatment. Minoxidil is rarely required in patients with advanced chronic kidney disease and its use requires some expertise in anticipating and managing side-effects of fluid retention. Combined alpha- and beta-blockers (e.g., carvedilol, labetolol) are considerations. Additionally, physicians with expertise in managing difficult patients have had niche success using a combination of a dihydropyridine calcium-channel blocker plus a nondihydropyridine calcium-channel blocker (e.g., amlodipine plus diltiazem). Clonidine is generally avoided because of its side-effect profile.

The most important principles for managing the challenging patient are:

1. Promotion of medication adherence using the principle of pill reduction (i.e., use of single pill, fixed-dose combination formulations or avoidance of twice-daily dose regimens when possible)
2. Maximising the dose of the diuretic
3. Use of spironolactone as a fourth drug when possible. [99] It is also important to question the patient's alcohol use and offer lifestyle counselling.

Referral to a specialist in hypertension should be considered.

Older adults

In very elderly patients, many physicians are reluctant to treat HTN in accordance with usual BP goals, for a number of reasons, including concerns about fall risk, drug interactions, adverse effects, and lack of benefit in mortality reduction. Previous literature reviews and meta-analysis demonstrated reductions in stroke, heart failure, and cardiovascular events in the very elderly without reaching mortality benefit. [100] [101] However, the SPRINT trial found that treating ambulatory adults aged 75 years or older to a SBP target of <120 mmHg (as measured by AOBP) resulted in significantly lower rates of fatal and non-fatal major cardiovascular events and death from any cause, compared with a SBP target of <140 mmHg. [66]

The American College of Cardiology Foundation/American Heart Association have published guidelines that suggest treating the very elderly carefully and with different BP goals from those previously recommended. [102] These guidelines recommend that medication be initiated at the lowest dose with gradual increments as tolerated. If BP remains

uncontrolled, a second drug from a different class should be added. The recommended target BP in people aged 80 years and older is BP <150/90 mmHg.

European guidelines recommend treating elderly persons with systolic BP ≥160 mmHg to a target of between 150 and 140 mmHg. [3] A goal of <140 mmHg may be considered for fit elderly persons younger than 80 years, whereas systolic BP goals should be adapted to individual tolerability in the fragile elderly population.

The JNC 8 guideline recommends initiating pharmacological therapy for patients ≥60 years at systolic BP ≥150 mmHg or diastolic BP ≥90 mmHg, and to treat to a systolic BP goal of <150 mmHg and a diastolic BP goal of <90 mmHg. [4]

Pregnancy

Treatment described in this monograph is for non-pregnant patients. Management in pregnancy should be referred to an obstetrician specialising in high-risk patients.

Implementation success

High levels of hypertension control in large multiethnic populations has been demonstrated using basic principles of implementation science. [103] [104] [105] Core principles include:

1. A comprehensive hypertension registry
2. An evidence-based hypertension treatment algorithm based on single pill combination therapy
3. Free medical assistant visits for blood pressure measurement with follow-up triage, and
4. Team-based performance reporting.

The use of 2-drug combination therapy, including single pill combination for patients with newly diagnosed hypertension with and without comorbidities, is consistent with the evidence-based JNC 8 guideline.

Given the large number of patients with hypertension and the use of protocol-based hypertension care delivery, team-based care incorporating nurses and clinical pharmacists is a key success factor. [106] [107] In team-based care collaboration, generally the role of the clinical pharmacist involves medication choice and delivery, and the role of the nurse is patient education. One RCT demonstrated the efficacy of a low cost nurse-led email reminder program across a spectrum of cardiovascular risk factors including lipid improvement and blood pressure reduction. [108]

The patient should be considered a hypertension team member. When a high risk group of patients with hypertension was randomised to self-monitoring and self-titration of antihypertensive medications versus usual care, 12 month reductions were 9.2/3.4 mmHg, favouring the self-care group. [109]

An important goal is to continue to make efforts to improve disparities in blood pressure control among people of different ancestries. [110]