Hypertension Treatment & Management

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Approach Considerations

Many guidelines exist for the management of hypertension. Two of the most widely used recommendations are those from the American Diabetes Association (ADA) and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). The Eighth Report of the JNC (JNC 8) was released in December 2013.[9, 10]

2013 updated JNC 8 guidelines

Two key recommendations in the JNC 8 guidelines that differ from the JNC 7 guidelines are (1) less aggressive targeting of blood pressures (BPs) and treatment-initiation thresholds for elderly patients and for those younger than age 60 years with diabetes and kidney disease and (2) no longer recommending only thiazide-type diuretics as the initial therapy in most patients (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], calcium channel blockers [CCBs], or diuretics are recommended).[9, 10]

The JNC 8 recommendations include the following[9, 10]:

- In patients aged 60 years or older, initiate therapy in those with systolic BP levels at 150 mm Hg or greater or whose diastolic BP levels are 90 mm Hg or greater; treat to below those thresholds
- In patients younger than 60 years as well as those older than 18 years with either chronic kidney disease (CKD) or diabetes, the BP treatment initiation and goals should be 140/90 mm Hg
- In nonblack hypertensive patients, begin treatment with either a thiazide-type diuretic, CCB, ACE inhibitor, or ARB
- In hypertensive black patients, initiate therapy with a thiazide-type diuretic or CCB
- Regardless of race or diabetes status, in patients 18 years or older with CKD, initial or add-on therapy should consist of an ACE inhibitor or ARB
- Do not use an ACE inhibitor in conjunction with an ARB in the same patient
- If a patient's goal BP is not achieved within 1 month of treatment, increase the dose of the initial agent or add an agent from another of the recommended drug classes; if 2-drug therapy is unsuccessful for reaching the target BP, add a third agent from the recommended drug classes
- In patients whose goal BP cannot be reached with 3 agents from the recommended drug classes, use agents from other drug classes and/or refer the patients to a hypertension specialist

Collaborative AHA/ACC/CDC advisory recommendations

A science advisory on the treatment of hypertension, issued in November 2013 via a collaborative effort by the American Heart Association (AHA), the American College of Cardiology (ACC), and the Centers for Disease Control and Prevention (CDC), describes criteria for successful hypertension management algorithms and advocates the creation of algorithms that can be incorporated into a system-level approach to high BP, as well as modified to accommodate different practice settings and patient populations.[59, 60]

A joint AHA/ACC/CDC algorithm in the report includes the following recommendations[59, 60]:

- BP: Recommended goal of 139/89 mm Hg or less
- Stage 1 hypertension (systolic BP 140-159 mm Hg or diastolic BP 90-99 mm Hg): Can be treated with lifestyle modifications and, if needed, a thiazide diuretic
- Stage 2 hypertension (systolic BP >160 mm Hg or diastolic BP >100 mm Hg): Can be treated with a combination of a thiazide diuretic and an ACE inhibitor, an angiotensin receptor blocker, or a calcium channel blocker
- Patients who fail to achieve BP goals: Medication doses can be increased and/or a drug from a different class can be added to treatment

Joint ESH and ESC guidelines

In June 2013, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) released new guidelines for the management of hypertension, recommending that all patients, except special populations such as patients with diabetes and the elderly, be treated to below 140 mm Hg systolic BP.[7, 8] The guidelines advise that physicians should make decisions on treatment strategies based on the patient's overall level of cardiovascular risk.

Recommendations of the new ESH and ESC guidelines include[7, 8]:

- In patients younger than 80 years, the systolic BP target should be 140 to 150 mm Hg, but physicians can go lower than 140 mm Hg if the patient is fit and healthy; the same advice applies to octogenarians—

however, the patient's mental capacity and physical heath should also be considered if targeting to less than 140 mm Hg
- Patients with diabetes should be treated to below 85 mm Hg diastolic BP
- Salt intake should be limited to approximately 5 to 6 g per day
- Body-mass index (BMI) should be reduced to 25 kg/m ^{2} and waist circumferences should be reduced to less than 102 cm in men and less than 88 cm in women
- Ambulatory BP monitoring (ABPM) should be incorporated into the assessment of risk
- Effective combination therapies include thiazide diuretics with ARBs, calcium-channel antagonists, or ACE inhibitors; or, calcium-channel antagonists with ARBs or ACE inhibitors
- Dual renin-angiotensin system blockade (ie, ARBs, ACE inhibitors, and direct renin inhibitors) is not recommended because of the risks of hyperkalemia, low BP, and kidney failure
- Although additional data is needed, renal denervation is a promising therapy in the treatment of resistant hypertension

ADA 2011 standard of medical care

The ADA 2011 standard of medical care states that in individuals with diabetes and mild hypertension, it may be reasonable to begin treatment with a trial of nonpharmacologic therapy (diet, exercise, and other lifestyle modifications.) Mild hypertension as defined by the ADA guideline (systolic BP 130-139 mm Hg or diastolic BP 80-89 mm Hg) may be classified as prehypertension by other organizations.[61]

The ADA 2011 standards of medical care in diabetes also indicate that a majority of patients with diabetes mellitus have hypertension. In patients with type 1 diabetes, nephropathy is often the cause of hypertension, whereas in type 2 diabetes, hypertension is one of a group of related cardiometabolic factors.[61, 62] Hypertension remains one of the most common causes of congestive heart failure (CHF). Antihypertensive therapy has been demonstrated to significantly reduce the risk of death from stroke and coronary artery disease.

Other studies have demonstrated that a reduction in BP may result in improved renal function. Therefore, earlier detection of hypertensive nephrosclerosis (using means to detect microalbuminuria) and aggressive therapeutic interventions (particularly with ACE inhibitor drugs) may prevent progression to end-stage renal disease.[12]

JNC 7

Key messages of the JNC 7 were as follows[3]:

- The goals of antihypertensive therapy is the reduction of cardiovascular and renal morbidity and mortality, with the focus on controlling the systolic BP, as most patients will achieve diastolic BP control when the systolic BP is achieved
- Prehypertension (systolic 120-139 mm Hg, diastolic 80-89 mm Hg) requires health-promoting lifestyle modifications to prevent the progressive rise in BP and cardiovascular disease
- In uncomplicated hypertension, a thiazide diuretic, either alone or combined with drugs from other classes, should be used for the pharmacologic treatment of most cases
- In specific high-risk conditions, there are compelling indications for the use of other antihypertensive drug classes (eg, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], beta blockers, calcium channel blockers)
- Two or more antihypertensive medications will be required to achieve goal BP (< 140/90 mm Hg or < 130/80 mm Hg) for patients with diabetes and chronic kidney disease
- For patients whose BP is more than 20 mm Hg above the systolic BP goal or more than 10 mm Hg above the diastolic BP goal, initiation of therapy using 2 agents, one of which usually will be a thiazide diuretic, should be considered
- Regardless of therapy or care, hypertension will be controlled only if patients are motivated to stay on their treatment plan

Lifestyle modifications

Lifestyle modifications are essential for the prevention of high BP, and these are generally the initial steps in managing hypertension. As the cardiovascular disease risk factors are assessed in individuals with hypertension, pay attention to the lifestyles that favorably affect BP level and reduce overall cardiovascular disease risk. A relatively small reduction in BP may affect the incidence of cardiovascular disease on a population basis. A decrease in BP of 2 mm Hg reduces the risk of stroke by 15% and the risk of coronary artery disease by 6% in a given population. In addition, a prospective study showed a reduction of 5 mm Hg in the nocturnal mean BP and a possibly significant (17%) reduction in future adverse cardiovascular events if at least one antihypertensive medication is taken at bedtime.

Surgical intervention

Aortorenal bypass using a saphenous vein graft or a hypogastric artery is a revascularization technique for renovascular hypertension that has become much less common since the advent of renal artery angioplasty with stenting. Surgical resection is the treatment of choice for pheochromocytoma and for patients with a unilateral solitary aldosterone-producing adenoma, because hypertension is cured by tumor resection. In patients with fibromuscular renal disease, angioplasty has a 60-80% success rate for improvement or cure of hypertension. A promising therapy for resistant hypertension is renal denervation via a percutaneous approach. This catheter-based intervention is currently in the clinical trial phase.

Consultations

Consultations with a nutritionist and exercise specialist are often helpful in changing lifestyle and initiating weight

loss. Consultations with an appropriate consultant are indicated for management of secondary hypertension attributable to a specific cause.

Nonpharmacologic Therapy

Lifestyle modifications

JNC 7 and AHA-ASA lifestyle modification recommendations

The Seventh Report of the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommendations to lower blood pressure (BP) and decrease cardiovascular disease risk include the following, with greater results achieved when 2 or more lifestyle modifications are combined[3] :

- Weight loss helps to prevent hypertension (range of approximate systolic BP reduction [SBP], 5-20 mm Hg per 10 kg); recommendations include the DASH (Dietary Approaches to Stop Hypertension) diet (range of approximate SBP reduction, 8-14 mm Hg), which is rich in fruits and vegetables and encourages the use of fat-free or low-fat milk and milk products
- Limit alcohol intake to no more than 1 oz (30 mL) of ethanol per day for men (ie, 24 oz [720 mL] of beer, 10 oz [300 mL] of wine, 2 oz [60 mL] of 100-proof whiskey) or 0.5 oz (15 mL) of ethanol per day for women and people of lighter weight (range of approximate SBP reduction, 2-4 mm Hg)
- Reduce sodium intake to no more than 100 mmol/d (2.4 g sodium or 6 g sodium chloride; range of approximate SBP reduction, 2-8 mm Hg) [6]
- Maintain adequate intake of dietary potassium (approximately 90 mmol/d)
- Maintain adequate intake of dietary calcium and magnesium for general health
- Stop smoking and reduce intake of dietary saturated fat and cholesterol for overall cardiovascular health
- Engage in aerobic exercise at least 30 minutes daily for most days (range of approximate SBP reduction, 4-9 mm Hg)

The 2010 American Heart Association-American Stroke Association (AHA-ASA) guidelines for the primary prevention of stroke makes the following recommendations:

- Hypertension: the AHA-ASA guidelines recommend regular blood pressure screening, lifestyle modification, and drug therapy; lower risk of stroke and cardiovascular events are seen when systolic blood pressure levels are lower than 140 mm Hg and diastolic blood pressure levels are less than 90 mm Hg
- In patients who have hypertension with diabetes or renal disease, the BP goal is lower than 130/80 mm Hg
- Diet and nutrition: a diet that is low in sodium and high in potassium is recommended to reduce BP; diets that promote the consumption of fruits, vegetables, and low-fat dairy products, such as the DASH-style diet, help lower BP and may lower the risk of stroke
- Physical inactivity: increasing physical activity is associated with a reduction in the risk of stroke; the goal is to engage in 30 minutes or more of moderate intensity activity on a daily basis
- Obesity and body fat distribution: weight reduction in overweight and obese persons is recommended to reduce BP and the risk of stroke

In a study that attempted to formulate a predictive model for the risk of prehypertension and hypertension, as well as an estimate of expected benefits from population-based lifestyle modification, investigators reported that the majority of risk factors have a larger role in prehypertension and stage 1 hypertension than in stage 2 hypertension. The investigators derived multistep composite risk scores by assessing significant risk factors in the progression from prehypertension to hypertension, as well as the regression of prehypertension to normal; they indicated that as the number of risk factors included in intervention programs increases, the size of the expected mean risk score decreases. In men, the 5-year predicted cumulative risk for stage 2 hypertension decreased from 23.6% (in the absence of an intervention program) to 14% (with 6-component intervention); the results were similar in women.

Dietary changes

A number of studies have documented an association between sodium chloride intake and BP. The effect of sodium chloride is particularly important in individuals who are middle-aged to elderly with a family history of hypertension. A moderate reduction in sodium chloride intake can lead to a small reduction in blood pressure. The American Heart Association recommends that the average daily consumption of sodium chloride not exceed 6 g; this may lower BP by 2-8 mm Hg.[6, 63]

One randomized controlled trial published found that moderate dietary sodium reduction (about 2500 mg Na^+ or 6 g NaCl per day) added to angiotensin-converting enzyme (ACE) inhibition was more effective than dual blockade (ACE inhibitor and angiotensin-receptor blocker [ARB]) in reducing both proteinuria and BP in nondiabetic patients with modest chronic kidney disease. Furthermore, a low-sodium diet added to dual therapy yielded additional reductions in both BP and proteinuria, emphasizing the beneficial effect of dietary salt reduction in the management of hypertensive patients with renal insufficiency.

The DASH eating plan encompasses a diet rich in fruits, vegetables, and low-fat dairy products and may lower blood pressure by 8-14 mm Hg. The 2011 ADA standard of care supports the DASH diet, with the caution that high-quality studies of diet and exercise to lower blood pressure have not been performed on individuals with diabetes.[61]

Dietary potassium, calcium, and magnesium consumption have an inverse association with BP. Lower intake of these elements potentiates the effect of sodium on BP. Oral potassium supplementation may lower both systolic and diastolic BP.[64] Calcium and magnesium supplementation have elicited small reductions in BP.

In population studies, low levels of alcohol consumption have shown a favorable effect on BP, with reductions of 2-4 mm Hg. However, the consumption of 3 or more drinks per day is associated with elevation of BP. Daily alcohol intake should be restricted to less than 1 oz of ethanol in men and 0.5 oz in women. The 2011 ADA standard supports limiting alcohol consumption in patients with diabetes and hypertension.[61]

Emerging evidence based on small randomized controlled trials suggests that dark chocolate may lower BP via improved vascular endothelial function and increased formation of nitric oxide. A meta-analysis of 13 randomized controlled trials that compared dark chocolate with placebo confirmed a significant mean SBP reduction of -3.2 mm Hg and DBP reduction of -2 mm Hg in hypertensive and prehypertensive subgroups.[65] However, several important questions needs to be answered before dark chocolate can be universally recommended as a lifestyle intervention.

First, whether the brand of dark chocolate makes a difference is unclear because studies using Ritter dark chocolate showed a change in BP, whereas Mars and Dove did not (although differences in study design limit direct comparison).[66] Second, the dose and time-dependent effects need to be further elucidated. Finally, the appropriateness of this intervention in diabetic, prediabetic, and/or overweight individuals needs to be balanced with the BP-reducing benefits.

Although many studies implicate a high fructose diet as a contributing factor to the metabolic syndrome and hypertension, a 2012 review of Cochrane database disputed this relationship.[67]

Weight loss and exercise

Up to 60% of all individuals with hypertension are more than 20% overweight. The centripetal fat distribution is associated with insulin resistance and hypertension. Even modest weight loss (5%) can lead to reduction in BP and improved insulin sensitivity. Weight reduction may lower blood pressure by 5-20 mm Hg per 10 kg of weight loss in a patient whose weight is more than 10% of ideal body weight.

Regular aerobic physical activity can facilitate weight loss, decrease BP, and reduce the overall risk of cardiovascular disease. Blood pressure may be lowered by 4-9 mm Hg with moderately intense physical activity.[3] These activities include brisk walking for 30 minutes a day, 5 days per week. More intense workouts of 20-30 minutes, 3-4 times a week, may also lower BP and have additional health benefits.[3]

Blumenthal et al found that in overweight or obese patients with high BP, adding exercise and weight loss to the DASH diet resulted in even larger reductions in BP and cardiovascular biomarkers of risk.[68] The trial showed that after 4 months, clinic-measured BP was reduced by 16.1/9.9 mm Hg in patients in the DASH-plus-weight management group; by 11.2/7.5 mm Hg in the DASH-alone group; and by 3.4/3.8 mm Hg in a control group eating a usual diet. Compared with DASH alone, DASH plus weight management also resulted in greater improvement in pulse wave velocity, baroreflex sensitivity, and left ventricular mass.[68]

The 2011 ADA diabetes standards support increasing physical activity. The recommendations emphasize that exercise is an important part of diabetes management in addition to reducing cardiovascular risk factors, contributing to weight loss, and improving overall well-being.[61] Moreover, patients with diabetes and severe hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg) at diagnosis or afterward should receive drug therapy along with lifestyle modifications.[61]

Pharmacologic Therapy

If lifestyle modifications are insufficient to achieve the goal blood pressure (BP), there are several drug options for the treatment and management of hypertension. Based on the Seventh Report of the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the 2010 Institute for Clinical Systems Improvement (ICSI) guideline on the diagnosis and treatment of hypertension recommendations, thiazide diuretics are the preferred initial agents in the absence of compelling indications.[3] However, the updated JNC 8 guidelines no longer recommend only thiazide-type diuretics as the initial therapy in most patients (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], calcium channel blockers [CCBs], or diuretics are also good choices).

Compelling indications may include high-risk conditions that can be direct sequelae of hypertension (heart failure, ischemic heart disease, chronic kidney disease, recurrent stroke) or that are commonly associated with hypertension (diabetes, high coronary disease risk), as well as drug intolerability or contraindications.[3] In such compelling cases, another class of drugs should be initiated. An ACE inhibitor, ARB, CCB, and beta-blocker are all acceptable alternative agents. There are several opinions regarding which antihypertensive agents to use initially, because some patients may respond to a therapy that others may not.

The following are drug class recommendations for compelling indications based on various clinical trials[3] :

- Heart failure: diuretic, beta-blocker, ACE inhibitor, ARB, aldosterone antagonist
- Postmyocardial infarction: beta-blocker, ACE inhibitor, aldosterone antagonist
- High coronary disease risk: diuretic, beta-blocker, ACE inhibitor, CCB
- Diabetes: diuretic, beta-blocker, ACE inhibitor, ARB, CCB
- Chronic kidney disease: ACE inhibitor, ARB
- Recurrent stroke prevention: diuretic, ACE inhibitor

Note that different stages of these diseases may alter their treatment management.

Multiple clinical trials suggest that most antihypertensive drugs provide the same degree of cardiovascular protection for the same level of BP control. Well-designed prospective randomized trials, such as the Swedish Trial

in Old Patients with Hypertension (STOP-2), the Nordic Diltiazem (NORDIL) trial, and the Intervention as a Goal in Hypertension Treatment (INSIGHT) trial, have shown that older drugs (eg, diuretics, beta-blockers) and newer antihypertensive agents (eg, ACE inhibitors, CCBs) have similar results.

In addition, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study concluded that there were no differences in primary coronary heart disease outcome or mortality for the thiazide-like diuretic chlorthalidone, the ACE inhibitor lisinopril, and the CCB amlodipine.[3] In a systematic review and meta-analysis, investigators also determined that in patients with essential hypertension without preexisting renal disease, no significant difference was found between Ras inhibitors and other antihypertensive agents in preventing renal dysfunction.

A post hoc analysis of data from the randomized ACCOMPLISH trial concluded that benazepril plus amlodipine (B+A) was more effective than benazepril plus hydrochlorothiazide (B+H) in reducing cardiovascular events in adults with high-risk stage 2 hypertension and coronary artery disease (CAD).[69, 70]

In this study, 5314 patients with CAD and 6192 without CAD were given B+A or B+H. Among patients with CAD, the incidence of cardiovascular events was 16% with B+H and 13% with B+A, a hazard reduction of 18% (P = 0.0016).[69, 70] The composite secondary endpoint of cardiovascular mortality, myocardial infarction, and stroke occurred in significantly fewer B+A patients than B+H patients (5.74% vs 8%; P = 0.033). All-cause mortality was 23% lower in the B+A arm (P = 0.042).

Single agent versus multiagent treatment approach

Over 50% of patients with hypertension will require more than one drug for blood pressure control.[5] In stage 1 hypertension, a single agent is generally sufficient to reduce BP, whereas in stage 2, a multidrug approach may be needed. Initiation of 2 antihypertensive agents, either as 2 separate prescriptions or as a fixed-dose combination, should also be considered when BP is more than 20 mm Hg above the systolic goal (or 10 mm Hg above the diastolic goal).[3]

Several situations demand the addition of a second drug, because 2 drugs may be used at lower doses to avoid the adverse effects that may occur with higher doses of a single agent. Diuretics generally potentiate the effects of other antihypertensive drugs by minimizing volume expansion. Specifically, the use of a thiazide diuretic in conjunction with a beta-blocker or an ACE inhibitor has an additive effect, controlling BP in up to 85% of patients.

The ALTITUDE trial was halted because it was shown that aliskiren can cause adverse events—nonfatal stroke, renal complications, hyperkalemia, and hypotension—when used in combination with an ACE inhibitor or an angiotensin receptor blocker (ARB) in patients with type 2 diabetes and renal impairment who are at high risk of cardiovascular and renal events.

Management of Diabetes and Hypertension

Hypertension is not only disproportionately high in diabetic individuals, but it also increases the risk of diabetes 2.5 times within 5 years in hypertensive patients.[3] In addition, hypertension and diabetes are both risk factors for cardiovascular disease, stroke, progression of renal disease, and diabetic retinopathy.[3]

For patients aged 18 years or older with diabetes, the 2013 Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) recommends initiating treatment at systolic blood pressure (BP) levels of 140 mm Hg or greater or at diastolic BP levels of 90 mm Hg or greater, and then treat to a goal BP below 140/90 mm Hg.[9, 10]

The JNC 7 and the 2011 American Diabetes Association (ADA) standard of medical care recommended blood pressure control in diabetic individuals be controlled to 130/80 mm Hg or lower, primarily to prevent or lower the risk of progression from diabetic nephropathy to end-stage renal disease.[3, 61]

This notion is being challenged by data from the ACCORD trial, which showed that in patients with type 2 diabetes, targeting an SBP of less than 120 mm Hg compared with less than 140 mm Hg did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.[17] A total of 4733 patients with type 2 diabetes were randomly assigned to intensive therapy or standard therapy, with a mean SBP of 119.3 mm Hg in the intensive group and 133.5 mm Hg in the standard group. No difference was observed in terms of primary outcome (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) and no difference was noted in annual rates of death from any cause.

However, annual rates of stroke, a prespecified secondary outcome, were significantly reduced in the intenstive therapy group (0.32% vs 0.53%). Serious adverse events attributed to antihypertensive treatment was signficantly greater in the intensive therapy group (3.3% vs 1.3%). Thus, other than a minor decrease in stroke rate, intensive BP control in diabetes did not improve outcome and was associated with a greater rate of serious adverse events.

In general, patients with diabetes type 1 or type 2 and hypertension have shown clinical improvement with diuretics, ACE inhibitors, beta-blockers, ARBs, and calcium antagonists.[3] Most studies, however, have shown superiority of ACE inhibitors or ARBs over calcium antagonists in diabetic patients. A notable exception is the ACCOMPLISH trial, which showed that, in patients at high risk for cardiovascular events, the combination of benazepril (an ACE inhibitor) and amlodipine (a CCB), was superior to the combination of benazepril plus hydrochlorothiazide (a thiazide diuretic).[71] About 60% of the patient cohort had diabetes.

Two or more antihypertensive drugs at maximal doses should be used to achieve optimal BP targets in patients with diabetes and hypertension.[61] Either an ACE inhibitor or an ARB is usually required in patients with diabetes and hypertension. If the patient cannot tolerate one class of drugs, the other should be tried. If needed to achieve

BP goals, a thiazide diuretic is indicated for those patients with an estimated GFR of 30 mL/min/1.73 m^2 or greater, and a loop diuretic is indicated for those with an estimated GFR of less than 30 mL/min/1.73 m^2. Regardless of which antihypertensive drugs are used, kidney function and serum potassium levels should be monitored.[61]

In a subgroup analysis from the TRINITY study (**TRI** ple therapy with olmesartan medoxomil, amlodipine, and hydrochlorothiazide in hyperte **N** sive patien **T** s stud **Y**), Chrysant et al reported that in patients with hypertension and diabetes, triple-combination drug therapy resulted in greater BP reductions and BP-goal achievement (< 130/80 mm Hg) than dual-combination drug therapy. The triple-combination regimen consisted of olmesartan medoxomil, 40 mg; amlodipine besilate, 10 mg; and hydrochlorothiazide, 25 mg.

Ruggenenti et al found that in patients with type 2 diabetes who have hypertension, combined manidipine and delapril therapy helped improve health in patients with cardiovascular disease, retinopathy, and neuropathy, as well as stabilized insulin sensitivity.[72] However, neither of these agents are available in the US.

A recent randomized, placebo-controlled study of 119 patients demonstrated that adding spironolactone to existing treatment in patients with resistant hypertension and diabetes mellitus significantly lowered blood pressure. Systolic and diastolic blood pressure were each significantly reduced in the spironolactone group and unchanged in the placebo group at 4 months.[73]

Management of Hypertensive Emergencies

Hypertensive emergencies are characterized by severe elevations in BP (>180/120 mm Hg) associated with acute end-organ damage.[3] Examples include hypertensive encephalopathy, intracerebral hemorrhage, acute myocardial infarction, acute left ventricular failure with pulmonary edema, aortic dissection, unstable angina pectoris, eclampsia,[3] or posterior reversible encephalopathy syndrome (PRES) (a condition characterized by headache, altered mental status, visual disturbances, and seizures).[49] Patients with hypertensive emergencies should be monitored and managed in an intensive care unit.[29, 74]

The primary goal of the physician is to determine which patients with acute hypertension are exhibiting symptoms of end-organ damage and require immediate intravenous parenteral antihypertensive therapy. That is, the fundamental principle in determining the necessary emergent care of the hypertensive patient is the presence or absence of end-organ dysfunction.

Initial treatment goals are to reduce the mean arterial BP by no more than 25% within minutes to 1 hour. If the patient is stable, reduce the BP to 160/100-110 mm Hg within the next 2-6 hours.[3] Several parenteral and oral therapies can be used to treat hypertensive emergencies, such as nitroprusside sodium, hydralazine, nicardipine, fenoldopam, nitroglycerin, or enalaprilat. Other agents that may be used include labetalol, esmolol, and phentolamine.[3] Avoid using short-acting nifedipine in the initial treatment of this condition because of the risk of rapid, unpredictable hypotension and the possibility of precipitating ischemic events.[3] Once the patient's condition is stabilized, the patient's BP may be gradually reduced over the next 24-48 hours.

Exceptions to the above recommendation include the following[3] :

- Patients with an ischemic stroke (currently, no clear evidence exists for immediate antihypertensive treatment)
- Patients with aortic dissection (their systolic BP should be lowered to < 100 mm Hg, if tolerated)
- Patients in whom BP is lowered to allow thrombolytic therapy (eg, stroke patients)

Approximately 3-45% of adult patients presenting to an emergency department have at least one increased BP during their stay in the ED, but only a small percentage of patients will require emergency treatment. However, medical therapy and close follow-up are necessary in patients who present to the ED with acutely elevated BPs (systolic BP >200 mm Hg or diastolic BP >120 mm Hg) that remain significantly elevated until discharge.[75]

For further information, see the Medscape Reference article Hypertensive Emergencies in Emergency Medicine.

Management of Hypertension in Pregnancy

In patients who are pregnant, the goal of antihypertensive treatment is to minimize the risk of maternal cardiovascular or cerebrovascular events. Hypertensive disorders—categorized as chronic hypertension, preeclampsia, chronic hypertension with superimposed preeclampsia, gestational hypertension, and transient hypertension (see Table 3, below)— may contribute to maternal, fetal, or neonatal morbidity and mortality, particularly in the first trimester.[3]

Table 3. Hypertensive Disorders in Pregnancy (Open Table in a new window)

Classification	Characteristics
Chronic hypertension	Prepregnancy or before 20 weeks' gestation; SBP =140 mm Hg or DBP 90 mm Hg that persists >12 weeks postpartum
Preeclampsia	After 20 weeks' gestation; SBP =140 mm Hg or DBP 90 mm Hg with proteinuria (>300 mg/24 h) Can progress to eclampsia

	More common in nulliparous women, multiple gestation, women with hypertension =4 years, family history of preeclampsia, previous hypertension in pregnancy, and renal disease
Chronic hypertension with superimposed preeclampsia	New-onset proteinuria after 20 weeks in hypertensive woman In a woman with hypertension and proteinuria before 20 weeks' gestation Sudden 2- to 3-fold increase in proteinuria Sudden increase in BP Thrombocytopenia Elevated AST or ALT levels
Gestational hypertension	Temporary diagnosis Hypertension without proteinuria after 20 weeks' gestation May be a preproteinuric phase of preeclampsia or a recurrence of chronic hypertension that abated in mid-pregnancy May lead to preeclampsia Severe cases may cause higher rates of premature delivery and growth retardation relative to mild preeclampsia
Transient hypertension	Diagnosis made retrospectively BP returns to normal by 12 weeks' postpartum May recur in subsequent pregnancies Predictive of future primary hypertension

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; DBP = diastolic BP; SBP = systolic BP.

Adapted from: Chobanian AV, Bakris GL, Black HR, et al, and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. Dec 2003;42(6):1206-52.[3]

In normal pregnancy, women's mean arterial pressure (MAP) drops 10-15 mm Hg over the first half of pregnancy. Most women with mild chronic hypertension (ie, systolic BP 140-160 mm Hg, diastolic BP 90-100 mm Hg) have a similar decrease in BP and may not require any medication during this period. Conversely, diastolic BP greater than 110 mm Hg has been associated with an increased risk of placental abruption and intrauterine growth restriction, and systolic BP greater than 160 mm Hg increases the risk of maternal intracerebral hemorrhage.

Lifestyle modifications are generally sufficient for the management of pregnant women with stage 1 hypertension who are at low risk for cardiovascular complications during pregnancy.{{Re1} Restrictions to lifestyle modifications may include aerobic exercise (theoretical increased preeclampsia risk from inadequate placental blood flow) and weight reduction, even in obese pregnant women. Reduction of sodium intake and avoidance of tobacco and alcohol use are similar to those for individuals with primary hypertension.[3]

Although the primary risk of chronic hypertension in pregnancy is development of superimposed preeclampsia, no evidence suggests that pharmacologic treatment of mild hypertension reduces the incidence of preeclampsia in this population.

Antihypertensive therapy should be started in pregnant women if the systolic BP is greater than 160 mm Hg or the diastolic BP is greater than 100-105 mm Hg. The goal of pharmacologic treatment should be a diastolic BP of less than 100-105 mm Hg and a systolic BP of less than 160 mm Hg.

Women who have preexisting end-organ damage from chronic hypertension or who have previously required multidrug therapy for BP control should have a lower threshold for starting antihypertensive medication (ie, >139/89 mm Hg) and a lower target BP (< 140/90 mm Hg). The JNC 7 recommendations are to continue antihypertensive medication as needed to control BP and to reinstate antihypertensive therapy when the SBP is 150-160 mm Hg or the DBP is 100-110 mm Hg.

Selection of antihypertensive medication

Although reducing maternal risk is the goal of treating chronic hypertension in pregnancy, it is fetal safety that largely directs the choice of antihypertensive agent. Methyldopa is generally the preferred first-line agent because of its safety profile.[3] Other drugs that may be considered include labetalol, beta-blockers, and diuretics. Data are limited regarding the use of clonidine and calcium antagonists in pregnant women with chronic hypertension; however, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor (ARB) antagonists should be avoided because of the risk of fetal toxicity and death.[3]

For further information, see the Medscape Reference articles Hypertension and Pregnancy, Preeclampsia, and Eclampsia.

Management of Hypertension in Pediatric Patients

According to Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), pediatric hypertension is defined as high BP that persists on repeated measurements, at the 95th percentile or higher for age, height, and sex.[3] More cases of chronic hypertension are seen in children who are obese, have inactive lifestyles, or have a family history of hypertension or cardiovascular disease.[3]

Lifestyle interventions should be initiated in all hypertensive children. When lifestyle modifications are inadequate for BP control or are unsuccessful in patients with more elevated BP, pharmacologic therapy must be considered.[3] In general, the selection of antihypertensive agents in children is similar to that in adults, but the doses are smaller and must be closely titrated. Extreme cautions are necessary with antihypertensive therapy in sexually active teenage girls and in those who are pregnant; angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) should not be used.

Continuous IV infusions are the most appropriate initial therapy in acutely ill infants with severe hypertension. The advantages of IV infusions are numerous; the most important advantage is the ability to quickly increase or decrease the rate of infusion to achieve the desired BP. As in patients of any age with malignant hypertension, care must be taken to avoid too rapid a reduction in BP, so as to avoid cerebral ischemia and hemorrhage. Premature infants, in particular, are already at increased risk because of the immaturity of their periventricular circulation. Because of the paucity of available data regarding the use of these agents in newborns, the choice of agent depends on the individual clinician's experience.

In a large study that evaluated the incidence of hypertension, associated risk factors, and the use of antihypertensive drugs in the neonatal intensive care unit (NICU) setting, the risk for hypertension was found to be greatest in neonates with a high severity of illness assessment, extracorporeal membrane oxygenation (ECMO), coexisting renal disorder, and renal failure.[76] Nearly 58% of infants received antihypertensive therapy, with a median duration of 10 days, and 45% received more than one agent. The most common antihypertensive drugs were vasodilators (64.2% of hypertensive neonates), followed by ACE inhibitors (50.8%), calcium channel blockers

(24%), and alpha- and beta-blockers (18.4%).[76]

For further information, see the Medscape Reference article Pediatric Hypertension.

Management of Hypertension in the Elderly

The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) recommends for patients aged 60 years or older, initiate therapy in those who have systolic blood pressure (BP) levels at 150 mm Hg or greater or whose diastolic BP levels are 90 mm Hg or greater and to treat to below those thresholds.[9, 10]

The classic trials for treatment of isolated systolic hypertension are the Systolic Hypertension in the Elderly Program (SHEP)[77] and the Systolic Hypertension in Europe (Syst-EUR)[78] studies. Systolic pressure continues to rise progressively throughout life, reaching the highest levels in later stages of life. By the age of 60 years, of those with hypertension, about two thirds have isolated systolic hypertension, and by the age of 75 years, nearly all hypertensive patients have systolic hypertension, of which three quarters of cases are isolated hypertension.[3] Furthermore, severe arteriosclerosis may lead to pseudohypertension. Isolated hypertension results in low cardiac output because of the decreased stroke volume and high peripheral resistance. This may reduce glomerular filtration further, which is why low activity of renal angiotensin aldosterone cascade is encountered in elderly individuals who are hypertensive.

Despite low plasma renin activity (PRA), blood pressure responds well to ACE inhibitor and ARB therapy. Low doses of diuretics may also be effective. Thiazide-type diuretics may be particularly beneficial for patients aged 55 years or older with hypertension or CVD risk factors and for patients aged 60 years or older with isolated systolic hypertension.[5] The SHEP trial found that chlorthalidone stepped-care therapy for 4.5 years was associated with a longer life expectancy at 22-year follow-up in patients with isolated systolic hypertension.[77] The Syst-Eur trial used a study design and sample size similar to those of the SHEP trial, in which treatment with the CCB nitrendipine resulted in significant reduction in stroke and overall CVD events.[78]

Calcium antagonists are quite useful because of their strong antihypertensive effects. Often, combining 2 drugs at a lower dose may be preferable to using a single drug at a high dose, because of the potential for adverse effects with the higher dose. Beta-blockers may not be as effective as other first-line agents in patients aged 60 years and older, especially for stroke prevention, and should probably be used when other indications are present, such as heart failure, previous myocardial infarction, and angina.[5]

Elderly patients should also be encouraged to lose weight if necessary, be more physically active, reduce their salt intake, and avoid excessive alcohol intake.[3]

AACF/AHA consensus opinion

According to the 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Expert Consensus Document on Hypertension in the Elderly, there are insufficient data supporting strong evidence-based guidelines on managing hypertension in older patients.[79] The ACCF/AHA document provides a consensus of expert opinion on clinical options; however, clinicians should take an individualized approach to the treatment of elderly patients.

The 2011 ACCF/AHA consensus document recommends doing 3 measurements of blood pressure (BP) to obtain an accurate BP value in the elderly patient with known or suspected hypertension.[79] If BP is elevated, the cause should be isolated. Any organ damage should be assessed. Other CVD risk factors or comorbid conditions should be identified, along with any potential barriers to treatment adherence.[79]

The consensus document also advises against the routine use of laboratory testing in elderly patients. Instead, it recommends a more deliberative, focused approach. This would include a urinalysis for signs of renal damage (albuminuria/microalbuminuria); blood chemistries (especially potassium and creatinine with estimated GFR); total cholesterol, LDL, HDL, and triglycerides; fasting blood sugar (A1c if diabetes mellitus is suspected); and an ECG.[79]

According to the ACCF/AHA consensus, lifestyle modifications may be all that is necessary to treat milder forms of hypertension in elderly patients.[79] However, drug treatment for elderly patients with hypertension is generally recommended and should be started at the lowest dose possible, with gradual increases depending on response.[79]

Management of Hypertension in Black Patients

For black patients, relative to non-Hispanic white persons, hypertension is more common and more severe, develops earlier, results in more clinical sequelae, and is associated with other comorbidities (eg, cardiovascular risk factors).[3] As with all prehypertensive and hypertensive patients, weight and sodium reduction (eg, DASH diet) can be effective for BP control.

The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) recommends initiating therapy with a thiazide-type diuretic or calcium channel blocker (CCB) in black patients with hypertension.[9, 10] In addition, regardless of race or diabetes status, in patients 18 years or older with CKD, initial or add-on therapy should consist of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) but not both (ie, do not use an ACE inhibitor and an ARB in the same patient).[9, 10]

Beta-blocker, ACE inhibitor, or ARB monotherapy in black patients may be less effective for BP reduction than in white patients.[3] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), thiazide-type diuretics or CCBs were more effective than ACE inhibitors in black patients. However, combination therapy with a diuretic and agents of the other drug classes eliminated the differences in BP reduction between racial groups.[3] In general, therapy is initiated at the lowest recommended dose of the selected agent; then, it is titrated upward, or another drug is added to reach the goal BP.[5]

In one study, Weinberger et al reported that the combination of aliskiren and amlodipine, a calcium channel blocker, was more effective than amlodipine alone in treating black patients with stage 2 hypertension and obesity or metabolic syndrome.[80] However, in December 2011, Novartis, the manufacturer of aliskiren, terminated the ALTITUDE study because of an increased incidence of adverse events (nonfatal stroke, renal complications, hyperkalemia, hypotension) when aliskiren was added to ACE inhibitor or ARB therapy. The study involved patients with type 2 diabetes and renal impairment at high risk for cardiovascular and renal events.

Management of Ocular Hypertension

Hypertension, especially stage 2 hypertension, can affect the retina, choroid, and optic nerve, as well as increase intraocular pressure (IOP).[3] In hypertensive retinopathy, the most common finding is generalized or focal narrowing of the retinal arterioles; occlusion or leakage of the retinal vessels may occur with acute or advanced hypertension. Hypertensive choroidopathy most commonly manifests in young patients with acute elevated blood pressure (BP), such as that which occurs in eclampsia or pheochromocytoma.[3]

Treatment of ocular hypertension varies. Depending on the severity of the ocular hypertension, management may include observation or initiation of antihypertensive therapy. In general, pharmacologic treatment is initiated in patients who have an increased risk of developing glaucoma.

Blood pressure control may result in regression of signs of hypertensive retinopathy, but spontaneous resolution may also be possible.[47] Among the issues that still need to be clarified are the following:

- Whether antihypertensive agents with potential direct beneficial microvascular effects (eg, ACE inhibitors) would reduce the damage of retinopathy beyond the reduction caused by lowered blood pressure
- Whether the specific reduction of hypertensive retinopathy also leads to reduction in cardiovascular disease morbidity and mortality
- Whether established risk-reducing interventions in targeted persons with hypertensive retinopathy would lead to additional advantages, as compared to the use of strategies without regard to retinal findings

In the presence of hypertensive optic neuropathy, a rapid reduction of BP may pose a risk of worsening ischemic damage to the optic nerve. The optic nerve demonstrates autoregulation, so there is an adjustment in perfusion based on BP. A precipitous reduction in BP will reduce perfusion to the optic nerve and central nervous system as a result of their autoregulatory changes, resulting in infarction of the optic nerve head and, potentially, acute ischemic neurologic lesions of the CNS.

For further information, see the Medscape Reference article Ocular Hypertension.

Management of Renovascular Hypertension

The goals of therapy for renovascular hypertension (RVHT) are maintenance of normal blood pressure (BP) and prevention of end-stage renal disease (ESRD). The therapeutic options include medical therapy, percutaneous transluminal renal angioplasty (PTRA) and stenting, and surgical revascularization. These options must be individualized, because no randomized studies document the superiority of one option over another.

It is important to note that the presence of renal artery stenosis or fibromuscular dysplasias are not always associated with renovascular hypertension. In addition, the potential benefits of percutaneous interventions are not proven. A trial by Bianchi et al failed to show improvement in systolic blood pressure, serum creatinine, renal events, mortality, or vascular events in patients with renal artery stenosis who underwent percutaneous renal artery intervention.[12]

In a study focusing on patients with atherosclerotic renal artery stenosis, data suggested that revascularization therapy should be confined to patients who have renal ischemia with viable underlying renal function, because they will experience the greatest clinical benefit. The indications for surgery or angioplasty include an inability to control BP while on a medical regimen, the need to preserve renal function, and intolerable effects of medical therapy.

With the advent of noninvasive techniques, aortal renal bypass using a saphenous vein or hypogastric artery is not commonly employed for revascularization. PTRA can be an effective treatment for hypertension and the preservation of renal function in a subset of patients. PTRA may be the initial choice in younger patients with fibromuscular lesions amenable to balloon angioplasty. Renal artery stenting of osteal lesions has been associated with improved long-term patency.

Medical therapy is required in the preoperative phase of interventional therapy. Medical therapy is also indicated for high-risk individuals and for older patients who have easily controlled hypertension. The specific population that will benefit from these techniques has yet to be clearly defined.

ACE inhibitors are effective in patients with unilateral renal artery stenosis; however, ACE inhibitors need to be avoided in patients with bilateral renal artery stenosis or stenosis of a solitary kidney. A diuretic can be combined with an ACE inhibitor. Because of their glomerular vasodilatory effect, calcium antagonists are effective in renal artery stenosis and do not compromise renal function.

For most patients with RVHT, with the exception of persons with fibromuscular dysplasia, it is unclear whether revascularization will be beneficial. Fibromuscular dysplasia responds well to angioplasty. The causes of renovascular hypertension include atherosclerosis, fibromuscular dysplasia, coarctation of the aorta, embolic renal artery occlusion, aneurysm of the renal artery, and diffuse arteritis. Additionally, causes of diffuse bilateral renal ischemia (eg, accelerated hypertension, vasculitis, hepatitis B, and IV drug abuse) may also lead to hypertension.

For further information, see the Medscape Reference article Renovascular Hypertension.

Management of Resistant Hypertension

Resistant hypertension is commonly defined as a blood pressure (BP) level higher than 140/90 mm Hg despite treatment with antihypertensive agents of 3 or more different classes, of which 1 is a thiazide diuretic. A study demonstrated that the addition of low-dose spironolactone provides significant additive BP reduction in both black patients and white patients who have resistant hypertension, with or without primary hyperaldosteronism.[81] However, ambulatory BP is normal in more than one third of patients with resistant hypertension, stressing the importance of monitoring patients to achieve correct diagnosis and management.[82]

Catheter-based renal sympathetic denervation is a novel investigational treatment for resistant hypertension (defined here as a SBP ≥160 mm Hg taking ≥3 antihypertensive drugs, including a diuretic). This treatment is based on the importance of renal sympathetic and somatic nerves in modulating blood pressure and the development of a novel procedure that selectively ablates these nerves. Originally published as a small, 45 patient proof of principle and safety study in 2009,[83] a follow-up study with 153 patients (Symplicity HTN-1) conducted in Australia, Europe, and the United States showed that this technique lowers BP for an extended period of up to 2 years.[84] Postprocedure office BPs were reduced by 20/10 mm Hg, 24/11 mm Hg, 25/11 mm Hg, 23/11 mm Hg, 26/14 mm Hg, and 32/14 mmHg at 1, 3, 6, 12, 18, and 24 months, respectively. The complication rate was 3% and consisted of 3 groin pseudoaneurysms and 1 renal artery dissection, all managed without further sequelae.

An open label prospective, randomized study conducted in 24 centers in Europe, Australia, and New Zealand (Symplicity HTN-2) confirmed the safety and efficacy of this treatment in 106 patients randomized to renal denervation with previous treatment (n=52) or to previous treatment alone (n=54).[85] Renal denervation resulted in a reduction in SBP of 10 mm Hg or more in 84% of patients, compared with 35% of controls. No serious procedure-related or device-related complications occurred. The Symplicity HTN-3 trial is ongoing and was designed as a prospective, randomized, masked, single-blind trial to evaluate the safety and effectiveness of catheter-based bilateral renal denervation for the treatment of resistant hypertension (defined as above).

In addition, data suggest baroreceptor activation treatment (BAT) by an implantable stimulator can potentially safely reduce SBP over the long term in patients with resistant hypertension.[86]

Causes of resistant hypertension

Causes of resistant hypertension include improper BP measurement, volume overload, drug-induced or other causes, and associated conditions such as obesity or excessive alcohol intake.

Improper BP measurement

Improper BP measurement may result in falsely high readings, such as when the wrong-sized cuff is used, when patients have heavily calcified or arteriosclerotic brachial arteries, or in cases of white-coat hypertension (observed in 20-30% of patients[53]).

In one study, investigators determined that a true diagnosis of resistant hypertension with ambulatory BP monitoring (ABPM) is associated with a more severe degree of vascular dysfunction (versus white-coat resistant hypertension), as measured by hyperemia-induced forearm vasodilation (HIFV) and serum biomarkers.[87] However, there is no direct association between BP levels and other types of abnormalities in vascular function (eg, compliance).[87]

Falsely high readings due to white-coat hypertension may be avoided by having patients rest before the measurement, by having a nurse check the blood pressure, or by arranging to have the blood pressure monitored at home. Development of hypotensive symptoms with the patient on medication is an indication of this type of hypertension. White-coat hypertension can also be evaluated by the use of a 24-hour ambulatory monitor.

Inadequate treatment and patient noncompliance

Inadequate treatment is common in cases of resistant hypertension[3] ; in several published series, this has been described as the most common cause of resistant hypertension. Patients may not be on an effective drug or drug dose, or concomitant volume expansion may occur as a side effect of the drug.

Noncompliance with medical therapy or dietary modifications (eg, salt restriction) may play a role in causing resistant hypertension. Address noncompliance with extensive patient education, simplification of the drug regimen, use of fixed-dose combinations, and use of drugs with the fewest adverse effects.

Limited data suggest better compliance with ACE inhibitors and ARBs than with some of the other antihypertensive medications.[88]

Extracellular volume expansion

Extracellular volume expansion may contribute to the inability to lower systemic BP. The volume expansion may occur because of renal insufficiency or because of sodium retention due to treatment with vasodilators, a high-salt diet, or insufficient dosing of a diuretic. This condition can be treated with more aggressive diuretic therapy until

clinical signs of extracellular volume depletion (eg, orthostatic hypotension) develop. The JNC 7 recommends a thiazide-type diuretic for the majority of hypertensive patients but notes that patients with a decreased GFR or who are in heart failure often require therapy with a loop diuretic.[3]

Vasoactive substances

Resistant hypertension may be encountered in patients who are ingesting vasoactive substances despite taking antihypertensive drugs regularly. Salt and alcohol are common examples; others include cocaine, amphetamines, anabolic steroids, oral contraceptives, cyclosporine, antidepressants, and nonsteroidal anti-inflammatory drugs.

Excluding secondary causes

Whenever confronted with resistant hypertension, try to exclude any secondary causes of hypertension. A reevaluation of the patient's history, physical examination, and laboratory results may provide clues to secondary hypertension (eg, renal artery stenosis, primary hyperaldosteronism, obstructive sleep apnea). Primary hyperaldosteronism is estimated to have a prevalence of 20% in this population.[89]

Obstructive sleep apnea is also associated with resistant hypertension, with 85% of patients with resistant hypertension having an elevated apnea/hypopnea index. A study by Pedrosa et al also found that 2 good predictors of sleep apnea in patients older than 50 years with resistant hypertension is a large neck circumference and snoring.[90]

However, treatment with CPAP may reduce BP in patients with resistant hypertension and sleep apnea. In the Spanish open-label, randomized HIPARCO trial, 98 patients with obstructive sleep apnea (OSA) and resistant hypertension who were treated with 12 weeks of continuous positive airway pressure (CPAP) had significantly improved 24-hour mean and diastolic blood pressure (BP) measurements, as compared to BP in 96 patients who did not receive CPAP therapy.[91, 92] Reductions in 24-hour mean and diastolic BP in the CPAP group were 3.1 mm Hg and 3.2 mm Hg, respectively, but there was no change in 24-hour systolic BP. However, a per-protocol analysis showed reductions in 24-hour mean BP (4.4 mm Hg) and diastolic BP (4.1 mm Hg) and a significant decrease in 24-hour systolic BP (4.9 mm Hg).[91, 92]

In addition, 35.9% of those on CPAP therapy showed improvements in their nocturnal BP pattern (ie, ≥10% decrease in average nighttime vs average daytime BP), as compared to 21.6% in the control group. There was also a significant correlation between duration of CPAP use and the reduction in BP levels.[91, 92]

Management of Pseudohypertension

Pseudohypertension in an overestimation of intra-arterial pressure by cuff blood pressure (BP) measurement. This may be observed in elderly individuals who have thickened, calcified arteries, as the cuff has relatively more difficulty compressing such arteries; much higher cuff pressure may be required to occlude a thickened brachial artery. The diastolic BP may also be overestimated.

Consider pseudohypertension in situations in which no organ damage occurs despite markedly high BP measurements, when patients develop hypotensive symptoms on medications, and when calcification of the brachial artery is observed on radiologic examination. Direct measurement of intra-arterial pressure may be required in this setting.

Management of Pheochromocytoma

Following suspicion of pheochromocytoma (labile, elevated blood pressure [BP]; paroxysmal hypertension with headache palpitations, pallor, perspiration),[3] the presence of a tumor should be confirmed biochemically by measuring urine and plasma concentrations of catecholamine or their metabolites. Keep in mind that catecholamine testing is subject to an increased rate of false positives, which can be due to medication effects or measurement conditions. In most situations, computed tomography scanning or magnetic resonance imaging may be used to localize the tumor in the abdomen. In the absence of abdominal imaging, nuclear scan with metaiodobenzylguanidine (MIBG) may further help with the localization. Positron emission tomography (PET) scanning and octreotide scanning may also be used.

Surgical resection is the treatment of choice for pheochromocytoma, because hypertension is cured by tumor resection. In the preoperative phase, nonspecific alpha-adrenergic blockade is indicated with phenoxybenzamine, and following adequate alpha-adrenergic blockade, beta-adrenergic blockade is added if excess tachycardia is present. These patients are often volume contracted and require saline or sodium tablets. Catecholamine production can be reduced further by metyrosine.

For adrenal pheochromocytoma, laparoscopic adrenalectomy is becoming the procedure of choice in suitable patients. Follow-up 24-hour urinary excretion studies of catecholamines should be performed 2 weeks following surgery (and periodically thereafter) to detect recurrence, metastases, or development of second primary lesion.

For further information, see the Medscape Reference article Pheochromocytoma.

Management of Primary Hyperaldosteronism

The prevalence of primary hyperaldosteronism increases with the severity of hypertension, being 2% in stage 1 and 20% in resistant hypertension.[89] Hypokalemia (an unprovoked or an exaggerated hypokalemic response to a thiazide) and metabolic alkalosis are important clues to the presence of primary hyperaldosteronism. However, these are relatively late manifestations; in a large subset of patients, the serum potassium concentration and

bicarbonate are within the reference range, and additional screening testing is needed in patients with high index of suspicion for primary hyperaldosteronism.

Measurement of the ratio of plasma aldosterone to renin activity ratio is the best initial screening test for primary hyperaldosteronism. A ratio of over 20-30 suggests that primary hyperaldosteronism may be present. Some labs require a minimum plasma aldosterone level of 12 ng/dL.

The diagnosis of primary hyperaldosteronism can be confirmed by the determination of the aldosterone excretion rate in a 24-hour urine following IV or oral salt loading (ie, urinary aldosterone excretion rate greater than 12-14 µg/24 hours, with urine sodium at least 200 mEq/24 hours). Saline suppression testing can also be used to confirm the diagnosis.

The appropriate therapy depends on the cause of excessive aldosterone production. A CT scan with dynamic protocol may help localize an adrenal mass, indicating adrenal adenoma, which may be a nonsecreting incidentaloma or a hypersecreting adenoma. If the results of the CT scan are inconclusive, adrenal venous sampling for aldosterone and cortisol levels should be performed.

Medical therapy is indicated in patients with adrenal hyperplasia, patients with adenoma who are poor surgical risks, and patients with bilateral adenomas. These patients are best treated with sustained salt and water depletion. Hydrochlorothiazide or furosemide in combination with either spironolactone or amiloride corrects hypokalemia and normalizes the blood pressure. Some patients may require the addition of a vasodilator or a beta-blocker for better control of hypertension.

Adrenal adenomas may be resected via a laparoscopic procedure. Surgical resection often leads to the control of blood pressure and the reversal of biochemical abnormalities. These patients may develop hypoaldosteronism during the postoperative follow-up period and require supplementation with fludrocortisone.

For further information, see the Medscape Reference article Hyperaldosteronism.

Interventions for Improving Blood Pressure Control

Various interventions can be implemented to improve BP control in patients with hypertension or to treat uncontrolled hypertension. These interventions include the following:

- Self-monitoring
- Educational interventions directed to the patient
- Educational interventions directed to the health professional
- Nurse or pharmacist care
- Organizational interventions that aim to improve the delivery of care
- Appointment reminder systems

The Cochrane Collaboration has shown that these interventions are associated with large net BP reductions and that health professional (nurse or pharmacist)–led care may be a promising way of delivering care. A study by Pezzin et al found that extensive patient education, coupled with nurse-led monitoring and feedback, resulted in significant improvements in 3-month BP control and secondary BP outcomes in high-risk black patients with stage 2 hypertension.[93] Cochrane recommendations include the recommendation that family practices and community-based clinics have an organized system of regular follow-up and review of their patients with hypertension. A randomized trial found that systolic BP decreased in individuals with poor BP control at baseline with use of home BP management consisting of nurse-administered behavioral management and nurse-administered and physician-administered medication management.[94]

Antihypertensive drug therapy should be implemented by means of a vigorous stepped care approach when patients do not reach target BP levels.

Prevention

A comprehensive strategy for reduction of mortality and morbidity associated with hypertension must include prevention strategies, earlier detection, and adequate treatment. Ideally, a population strategy should be used to lower BP in the community. More intensive efforts are required to lower blood pressure in high-risk population groups, which include individuals with a family history of hypertension, black ancestry, obesity, excessive sodium consumption, physical inactivity, and/or alcohol consumption. Even a small reduction in BP confers significant health benefits. A reduction of 2 mm Hg in diastolic BP is estimated to decrease the risk of stroke by 15% and the risk of coronary heart disease by 6%.

Prevention of hypertension may be achieved by the following interventions:

- Weight control
- Increased physical activity
- Moderated sodium and alcohol intake
- Increased potassium intake
- A diet rich in fruits and vegetables and low-fat meat, fish, and dairy products

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