

Hypertension Therapy Update

“Hypertension Therapy Update” is the first in a series of continuing education articles authored and generously contributed to the Tennessee Pharmacists Association by:

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1.5 Credit Hours (0.15 CEU)

Educational Goal

- The goal of this lesson is to discuss hypertension and its medical management.

Objectives

After completing this knowledge-based program, the participant will be able to:

- List goals for hypertension control;
- Chart categories of drug therapy available for hypertension treatment;
- Describe the use of each agent, dosing, and monitoring guideline;
- Forecast potential direction for future hypertension therapy plans.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7 Report) identifies evidence-based treatment steps for the management of hypertension. Blood pressure has been classified into 4 stages; normal (<120/80 mm Hg), prehypertension (120-139/80-89 mm Hg), stage 1 hypertension (140-159/90-99 mm Hg), and stage 2 hypertension (>160/>100 mm Hg). Diagnosis and classification of hypertension are determined from the average of 2 blood pressure readings obtained from 2 separate clinic visits; it is measured with the patient in a seated position, after at least a 5 minute rest. According to JNC-7 guidelines, the blood pressure goal in hypertensive patients without diabetes or any additional compelling conditions is less than 140 mm Hg systolic and less than 90 mm Hg diastolic, or less than 130 mm Hg systolic and less than 80 mm Hg

diastolic in patients with diabetes or chronic kidney disease. Depending on the presence of other comorbid conditions, the individualized goal may be lower. Treatment plans for hypertension have evolved to include combination therapy that targets different mechanisms to obtain optimal levels in blood pressure and possibly limit side effects.

Although the JNC-7 is the most recent report of recommendations, it was released in 2003, and new products and clinical evidence indicate some change will occur with the next review, the JNC-8. The indication from the Joint National Committee website (www.nhlbi.nih.gov/guidelines/hypertension/) is that the JNC-8 will not be released until 2011. One possible direction for the next review may be to recommend combination antihypertensive therapies very early in the treatment plan for a patient with

high blood pressure, rather than maximizing the dose of one drug at a time. The role of diuresis, and thiazide diuretics specifically, continues to be a topic of debate with each set of new guidelines. Diuretics improve the efficacy of the other agents for hypertension by limiting fluid retention. Some evidence suggests long term diuretic use may not result in optimal outcomes when compared to other combinations. Another potential shift may be a change in the goal blood pressure levels. The recent ACCORD blood pressure study demonstrated that tight management of blood pressure did not result in improved outcomes in patients with type 2 diabetes. The study design called for the intensively treated group to achieve a systolic blood pressure of <120 mm Hg, and the control group to achieve a systolic blood pressure of <140 mm Hg. A review of the data shows that the average systolic blood pressure achieved in the intensive treatment group was 119 mm Hg and 133 mm Hg in the control group. These results translate into positive outcomes in diabetic patients, due to their systolic blood pressure goal of less than 130 mm Hg.

Blood pressure is the product of cardiac output and total peripheral resistance (TPR). Cardiac output is the product of the stroke volume and heart rate. Pathophysiologic changes that result in hypertension are usually not limited to one abnormality; rather, several changes in the normal function of body systems contribute to the hypertensive condition. Two important systems that work to maintain normal blood pressure are the autonomic nervous system and the renin-angiotensin-aldosterone system. The autonomic nervous system maintains regulatory action for the vascular system. Abnormal sympathetic/adrenergic tone contributes to increased peripheral resistance. As a patient challenges his or her vascular system with increased fluid and sodium, renin activity in the kidney, a primary component of compensation, adjusts to the increased volume. Inhibition of renin reduces blood pressure and can reverse albuminuria.

The renin-angiotensin-aldosterone system regulates the balance of fluid volume, electrolytes, and blood volume in the body. Altered/decreased levels of fluid or sodium in the distal tubule of the nephron in the kidney stimulate the release of renin, which activates angiotensinogen to form angiotensin-I (AT-I). Angiotensin-converting enzyme (ACE), in the pulmonary and vascular

endothelium, then converts AT-I to angiotensin-II (AT-II). Aldosterone is released from the adrenal gland to induce retention of sodium and water with the goal of maintaining proper fluid and electrolyte balance. However, this renin activity also produces vasoconstriction, sodium retention, smooth muscle proliferation, and increased antidiuretic hormone in the vasculature. The real concern is that abnormally high renin activity is required to maintain balance. While some diseases can cause high renin activity, no specific cause other than poor health habits (high caloric and sodium intake, stressful lifestyle, tobacco use) can be identified in the majority of patients. Abnormally high release of renin over time can result in intraglomerular hypertension, with resulting proteinuria. These changes are chronic in nature and result in endothelial dysfunction and microalbuminuria. Insulin resistance is also a by-product of this long term assault on the kidney.

Therapy of Hypertension

Lifestyle modification should be the initial step of hypertension therapy for all patients. This treatment includes a meal plan such as the DASH (Dietary Approaches to Stop Hypertension) diet that limits sodium intake and facilitates healthy eating. Regular physical activity, according to each individual patient's tolerance level and comorbid conditions, should be included, as should possible weight reduction and stress relief. Smoking cessation, if needed, is also a valuable addition to the treatment plan. All healthcare providers should be prepared to assist and reinforce the message about these health habits.

Several different categories of antihypertensive medications with varying mechanisms are marketed. Today, the clinician can choose from a variety of products that may provide enhanced effects for the specific patient while limiting the side effect of the treatment. Table 1 provides a listing of the medication categories, products, and their dosing.

Types of Anti-hypertensive Medications

The diuretics clinically used for hypertension include thiazide-type, loop, and potassium-sparing agents, and the decision of which to use is based on their mechanism and/or site of action. Baseline renal function and serum potassium are important factors in determining the initial choice of diuretic. Thiazide diuretics are usually the initial or second

agent used for hypertension. Combination therapy with other preferred antihypertensive agents work synergistically to minimize the fluid retention of other therapies. The JNC-7 report recommends thiazide-type diuretics as first-line therapy for uncomplicated hypertensive patients.

Hydrochlorothiazide (HCTZ) is the most frequently prescribed diuretic for the treatment of hypertension alone, though not effective in patients with significant decline in renal function. Loop diuretics are the choice diuretic when the patient's glomerular filtration rate (GFR) falls below 30 mL/min, or in a situation where greater diuresis is needed, specifically in a volume overloaded patient with symptomatic heart failure. Potassium-sparing diuretics are the only diuretics that may increase serum potassium; loop and thiazide diuretics typically lower serum potassium based on their site of action. Clinically, potassium-sparing diuretics are combined with a thiazide-type diuretic to balance serum potassium. Alone, these medications have minimal effect on reducing blood pressure.

The various types of diuretics work in different areas of the kidney. Thiazide-type diuretics inhibit the Na⁺/Cl⁻ channel in the distal convoluted tubule of the nephron, whereas loop diuretics inhibit the Na⁺/K⁺/2Cl⁻ action in the ascending limb of the loop of Henle. Potassium sparing agents, amiloride and triamterene inhibit the luminal Na⁺ channels, while spironolactone and eplerenone are aldosterone antagonists. Initially, the drop in blood pressure from diuretics is due to a decreased cardiac output as a result of decreased blood volume. Chronically, the blood pressure reduction is not a result of diuresis.

Diuretics are generally taken once daily in the morning to limit sleep disruption from frequent urination, which can be caused by dosing diuretics in the evening. Low doses are used for the initial therapy and can be titrated up if necessary. For example, when treating hypertension alone, doses >25mg of HCTZ show no additional decrease in blood pressure.

Patients with preexisting gout or uric acid stone disease, severe renal impairment, hepatic dysfunction, and/or electrolyte imbalances require close monitoring, as diuretics can induce flare-ups/worsening of these disorders. Thiazide-type diuretics (except metolazone) are contraindicated in

patients with a known hypersensitivity to sulfonamides, though the risk of cross-sensitivity is not well defined. Adverse effects associated with diuretics can include changes in serum electrolytes, such as hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia, hyperlipidemia, hypercalcemia (thiazides), and hypocalcemia (loop). Photosensitivity has been reported. Some drug interactions of significance include nonsteroidal anti-inflammatory drugs (NSAIDs), which can decrease the antihypertensive effect of diuretics. Diuretics can substantially increase lithium levels by inhibiting lithium's elimination; therefore, lithium levels should be monitored 5 to 7 days after starting or discontinuing a diuretic. Thiazide diuretics are known to inhibit the release of insulin from the beta cells of the pancreas, resulting in hyperglycemia. Baseline blood pressure, serum electrolytes, uric acid, glucose, and lipids should be measured prior to initiating therapy, after 1-2 months, and every 6-12 months thereafter.

An angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) is recognized as a step one or a step two drug following a diuretic treatment. This staging is dependent on the patient's other compelling indications for therapy, such as chronic kidney disease, diabetes mellitus, heart failure, post-MI, or recurrent stroke prevention. ACE inhibitors can delay the progression of microalbuminuria to macroalbuminuria.

ACE inhibitors inhibit the formation of angiotensin-II by blocking the conversion of angiotensin-I to angiotensin-II. These agents increase bradykinin, which stimulates release of nitric oxide, a vasodilator. ACE inhibitors cause dilation of the efferent arteriole in the renal circulation, which aids in the lowering of blood pressure and long term renoprotective action but can also reduce GFR and induce acute renal failure. ARBs are traditionally prescribed when ACE inhibitor therapies are not tolerated due to side effects such as cough. ARBs inhibit angiotensin-II release by blocking the Angiotensin-I receptor. This leads to a reduction in aldosterone secretion, vasoconstriction, and sympathetic activity. ACE inhibitors are often less effective at lowering blood pressure and may increase the risk of angioedema in African-Americans.

ACE inhibitors and ARBs are generally administered 1 to 3 times daily with or without food. Once-daily dosing can be in the morning or evening, based on patient preference and adverse effects, such as drowsiness. Taking the medication at the same time every day is important. Concurrent food intake may affect the absorption of captopril and moexipril, so dosing prior to a meal is warranted. The effects of blood pressure lowering can be seen within 1 hour of administration, with maximum effects after 6 to 8 hours. ACE inhibitors and ARBs are contraindicated during pregnancy. Use in the second or third trimesters can lead to fetal injury or death.

Overall, ACE inhibitors are well tolerated with few side effects, especially if monitored appropriately. The most notorious adverse effect, often the reason for discontinuation of ACE inhibitors, is cough. This adverse effect is primarily due to the increase in bradykinin activity. Other adverse effects commonly associated with ACE inhibitors include fatigue, headache, dizziness, hyperkalemia, acute hypotension, and gastrointestinal problems. Hematologic effects, such as neutropenia and agranulocytosis, have also been reported. Concurrent use of NSAIDs, potassium-sparing diuretics, and potassium supplements may increase potassium levels. ACE inhibitors can increase lithium levels, due to decreased fluid volume and loss of sodium ions; therefore, close monitoring of lithium levels is recommended. Blood pressure, serum electrolytes, and renal function should be measured at baseline, in the first month, and every 6 months throughout treatment. ARBs are listed as category C for the first trimester of pregnancy and category D for the second and third trimesters, so ARBs should be avoided in pregnancy. ARBs are contraindicated in patients with significant disease of a single, functional kidney.

ARBs are generally well tolerated, with more common adverse effects including dizziness, diarrhea, dyspepsia, hyperkalemia, headache, and upper respiratory complaints. The frequency of cough associated with ARBs is less than with ACE inhibitors. Concurrent use of potassium-sparing diuretics, potassium supplements, or salt substitutes may increase serum potassium levels significantly. Use of ACE inhibitors and/or beta-blockers with ARBs should be avoided in patients with heart failure. ARBs can increase lithium levels due to

decreased fluid volume and loss of sodium ions; therefore, close monitoring of lithium levels is recommended. Blood pressure, serum electrolytes, and renal function should be measured at baseline and periodically throughout treatment. Potassium levels should be monitored within the first month of initial therapy and every 4-6 months, due to the potential onset of hyperkalemia.

Direct renin inhibitors (DRIs) are a relatively new category of agents for hypertension. They work within the renin-angiotensin-aldosterone system. This category is not included in the JNC-7, as it was introduced after the release of JNC-7. DRIs directly inhibit renin, which means that little or no contribution will result from the renin-angiotensin-aldosterone-system. Aliskiren is taken once daily and can be taken with or without food. Starting therapy begins with a low dose and is adjusted to goal. Adding an ARB or diuretic to aliskiren can be helpful in lowering blood pressure. DRIs are contraindicated in pregnancy. They have a low adverse effect profile that includes a cough, though the incidence is less than with ACE inhibitors. Diarrhea, dizziness, headache, rash, edema, increased uric acid, and low blood pressure can occur. Aliskiren is metabolized in the liver by the cytochrome P-450 3A4 system, and patients' blood pressure, electrolytes, and renal function should be monitored while on aliskiren.

Beta-blockers are commonly prescribed as an addition to an existing hypertension treatment plan. Beta-blockers are beneficial for patients with concurrent cardiac problems and are indicated for patients with high risk for coronary disease, as well as secondary prevention of MI and heart failure. There are 2 main types of beta-adrenergic receptors in human physiology, beta₁ and beta₂. Beta₁ receptors are located on the heart, where activation causes an increase in heart rate, contractility, and conduction velocity. Blockade of these receptors reduces cardiac output. The agents with combined alpha and beta blockade will be considered here with their improved lipid profile.

Beta-receptors have a wide range of functions in the body. Activation of beta₁-receptors located in the juxtoglomerular cells of the kidney stimulate the release of renin. Beta₂-receptors in the liver increase hepatic-mediated glucose output when stimulated. Beta₂-receptors in the lungs induce

bronchodilation. Some beta blockers are selective for beta₁ effect while others are nonselective and inhibit both the beta₁ and beta₂ receptors equally. When higher doses of a beta₁-selective blocker are given, selectivity diminishes. Highly lipid-soluble beta₁-receptor blockers cross the blood brain barrier readily and increase the risk of central nervous system adverse effects. Some beta-blockers also have intrinsic sympathomimetic activity (ISA). Beta-blockers are administered once to twice daily and should be taken at a consistent time.

Atenolol is classified as pregnancy category D and crosses the placental barrier, producing a reduced weight of infants. Beta-blockers are contraindicated in patients with sinus bradycardia. Nonselective beta-blockers are contraindicated in patients with asthma. Beta-blockers can inhibit the release of insulin from the pancreas, resulting in increased blood glucose levels in patients with type 2 diabetes. Conversely, they can also mask hypoglycemic-induced tachycardia, as it can decrease the individual's awareness of hypoglycemia, which typically presents as dizziness and sweating but may not be visible when a patient is on beta-blocker therapy.

Common adverse effects with beta-blockers are CNS-related, such as sedation, dizziness, drowsiness, lightheadedness, fatigue, and headache. Other notable adverse effects include bradycardia, hypotension, depression, and sexual dysfunction, especially in older adults. Gastrointestinal effects of constipation, diarrhea, and nausea have been reported but occur less frequently. Beta-blockers have additive effects on heart muscle contractility with nondihydropyridine calcium channel blockers (Diltiazem and Verapamil), amiodarone, and digoxin. Typically, patients taking beta-blockers should be tapered down when they are discontinued and not stopped suddenly. Baseline blood pressure, heart rate, lipid profile, and blood glucose levels should be conducted. Beta-blockers can increase total cholesterol, LDL-cholesterol, and triglycerides and decrease HDL-cholesterol.

Calcium channel blockers (CCBs) are an additional group of agents for hypertension control. Typically, they are a second or third option, and have less of an impact on cardiovascular disease when compared to other antihypertensive agents. Nondihydropyridine CCBs can be considered for

patients who have not tolerated ACE inhibitor or ARB therapy. Nondihydropyridine CCBs may reduce proteinuria. CCBs are structurally classified as nondihydropyridine and dihydropyridine. CCBs block the L-type calcium channel, which results in vasodilation. Nondihydropyridine CCBs primarily cause vasodilation within coronary vessels and have a more depressive effect on cardiac conduction, while dihydropyridine CCBs primarily cause vasodilation in the vascular smooth muscle. CCBs are dosed 1 to 3 times daily and can be taken with food to minimize adverse effects. Low initial dosage is adjusted every 2 weeks to patient tolerance, blood pressure, and heart rate. An immediate-release dosage form is rarely used for the treatment of hypertension. Typically, once-daily calcium channel blocker formulations are dosed in the morning, except for verapamil extended-release products, which are given at bedtime.

CCBs are also contraindicated in patients with sick sinus syndrome or a heart block without a pacemaker. Verapamil is contraindicated in patients with congestive heart failure. CCBs can induce headache, dizziness, nausea, dyspepsia, flushing, and constipation. Nondihydropyridine CCBs are associated with cardiac adverse effects including cardiac conduction abnormalities and bradycardia. Dihydropyridine CCBs have adverse effects related to their relaxing of vascular tone. Dihydropyridine CCBs cause peripheral edema more significantly than the other CCBs. Most CCB drug interactions stem from the cytochrome P-450 enzyme system. Concurrent medications and foods (such as grapefruit juice) that are also metabolized through this system should be used cautiously. Diltiazem and verapamil can inhibit other CYP3A4 substrates, such as statins and theophylline. CCBs inhibit platelet function, resulting in an increased risk for bleeding if used concurrently with anticoagulants, such as warfarin or aspirin.

Although indicated for the treatment of hypertension, alpha₁-receptor blockers are rarely prescribed for this indication. They are most beneficial in patients with benign prostatic hyperplasia (BPH). Alpha₁-receptor blockers can be a treatment option for patients with both diabetes and BPH. The alpha₁-receptor blockers inhibit the effect of norepinephrine on vascular alpha₁-receptors. Activation of the alpha₁-receptor by norepinephrine leads to vasoconstriction, resulting

in an increase in TPR. The α_1 -receptor blockers are preferably dosed at bedtime to minimize the risk of postural hypertension often observed within hours after administration. Initial therapy often starts with a lower dose and can be adjusted to goal.

The α_1 -receptor blockers also cause a mild decrease in neutrophils and white blood cell counts, which is generally not significant. Adverse effects commonly associated with α_1 -receptor blockers include fatigue, malaise, dizziness, shortness of breath, hypotension, edema, and weight gain; palpitations, blurred vision and sexual dysfunction have also been noted. Blood pressure and heart rate should be monitored at baseline and at each visit after initiating treatment. If antihypertensive agents are added, the patient should be assessed for first-dose syncope and postural hypotension.

Interruptions in therapy increase the risk; thus, nonadherent patients are not good candidates for this drug. Syncope is managed by having the patient lie down, rest, and receive supportive care as necessary.

Vasodilators induce their action by direct vasodilation of the vascular smooth muscle, producing a significant reduction in peripheral resistance. A reflex action from the baroreceptors to this action is an increase in heart rate, cardiac output and renin release. Candidates for vasodilators should receive diuretics and an agent that reduces adrenergic tone, perhaps a beta-blocker. Side effects include an increased heart rate, water retention, and dermatitis, and some cases report a peripheral neuropathy. Hydralazine may induce a dose-related, reversible lupus-like syndrome. Minoxidil can cause a hypertrichosis reaction.

While indicated for the treatment of hypertension, central-acting alpha-adrenergic agonists are rarely prescribed for this indication. Central-acting alpha-adrenergic agonists stimulate α_2 -receptors in the brain to inhibit the production of serotonin, dopamine, norepinephrine, and epinephrine. This inhibition produces decreased heart rate and TPR. Central-acting alpha-adrenergic agonists are available in tablets and a transdermal patch (Catapres[®]). Tablets are taken in daily divided doses, preferably at consistent times. Transdermal patches are applied once weekly. Clonidine is classified as pregnancy category C and should be

avoided. Methyldopa is pregnancy category B and can be used in pregnancy. It is converted to alpha-methylnorepinephrine, a natural by-product of catecholamine breakdown, which may also limit its use in gestation. The use of a monoamine oxidase inhibitor (MAOI) is contraindicated in patients taking methyldopa as hypertensive crisis reactions have been reported. Central-acting alpha-adrenergic agonists are contraindicated in patients with severe coronary insufficiency, recent MI, cerebrovascular disease, and renal or hepatic dysfunction. Side effects can include nausea, vomiting, constipation, dry mouth, and CNS-related effects, such as sedation, weakness, nervousness, dizziness, and drowsiness. Hypotension, sexual dysfunction, and hair thinning/loss have been reported.

Iron can decrease the absorption of methyldopa up to 66%. Therefore, iron should be separated by at least 2 hours from methyldopa administration. Methyldopa also increases the risk of lithium toxicity, even in the presence of normal lithium levels. Signs and symptoms of lithium toxicity, such as lethargy and muscle weakness, should be monitored. Over-the-counter drug products containing pseudoephedrine and ma huang (ephedra, ephedrine) can increase blood pressure. This is greatly enhanced for patients taking-methyldopa and clonidine. Tricyclic antidepressants, e.g., amitriptyline and imipramine, may antagonize central α_2 -receptors. Clonidine and methyldopa should also be used cautiously with beta-blockers, since withdrawal of these agents in patients concurrently on beta-blockers has led to life-threatening increases in blood pressure. Patients should be monitored for signs of depression at clinician visits. When stopping the drug, gradual tapering of the drug should occur over several days to prevent withdrawal.

Summary

Several agents are now marketed to control blood pressure to the desired range. However, little improvement in overall control has been noted, and further efforts are needed to encourage patients to continue to follow proper meal plans, engage in regular physical activity, and take their medications. Continual patient instruction about emerging techniques is vital. The future changes and updated recommendations brought forth by the JNC-8 will be interesting to observe.

Table 1 Oral Hypertensive Drugs

Class	Drug (Trade Name)	Usual Dose Range in Mg/Day	Usual Daily Frequency
Thiazide diuretics	chlorothiazide (Diuril)	125-500	1-2
	chlorthalidone (generic)	12.5-25	1
	hydrochlorothiazide (Microzide, HydroDIURIL)	12.5-50	1
	polythiazide (Renese)	2-4	1
	indapamide (Lozol)	1.25-2.5	1
	metolazone (Mykrox)	0.5-1.0	1
	metolazone (Zaroxolyn)	2.5-5	1
Loop diuretics	bumetanide (Bumex)	0.5-2	2
	furosemide (Lasix)	20-80	2
	torseamide (Demadex)	2.5-10	1
Potassium-sparing diuretics	amiloride (Midamor)	5-10	1-2
	triameterene (Dyrenium)	50-100	1-2
Aldosterone receptor blockers	eplerenone (Inspra)	50-100	1-2
	spironolactone (Aldactone)	25-50	1-2
Beta Blockers	atenolol (Tenormin)	25-100	1
	betaxolol (Kerlone)	5-20	1
	bisoprolol (Zebeta)	2.5-10	1
	metoprolol (Lopressor)	50-100	1-2
	metoprolol extended release (Toprol XL)	50-100	1
	nadolol (Corgard)	40-120	1
	propranolol (Inderal)	40-160	2
	propranolol long-acting (Inderal LA)	60-180	1
	timolol (Blocadren)	20-40	2
BBs with intrinsic sympathomimetic activity	acebutolol (Sectral)	200-800	2
	penbutolol (Levitol)	10-40	1
	pindolol (generic)	10-40	2
Combined alpha- and BBs	carvedilol (Coreg)	12.5-50	2
	labetalol (Normodyne, Trandate)	200-800	2
Direct Renin Inhibitors	aliskiren (Tekturna)	150-300	1
ACEIs	benazepril (Lotensin)	10-40	1
	captopril (Capoten)	25-100	2
	enalapril (Vasotec)	5-40	1-2
	fosinopril (Monopril)	10-40	1
	lisinopril (Prinivil, Zestril)	10-40	1
	moexipril (Univasc)	7.5-30	1
	perindopril (Aceon)	4-8	1

Class	Drug (Trade Name)	Usual Dose Range in Mg/Day	Usual Daily Frequency
	quinapril (Accupril) ramipril (Altace) trandolapril (Mavik)	10-80 2.5-20 1-4	1 1 1
Angiotensin II antagonists	candesartan (Atacand) eprosartan (Teveten) irbesartan (Avapro) losartan (Cozaar) olmesartan (Benicar) telmisartan (Micardis) valsartan (Diovan)	8-32 400-800 150-300 25-100 20-40 20-80 80-320	1 1-2 1 1-2 1 1 1-2
CCBs—non-Dihydropyridines	diltiazem extended release (Cardizem CD, Dilacor XR, Tiazac) diltiazem extended release (Cardizem LA) verapamil immediate release (Calan, Isoptin) verapamil long acting (Calan SR, Isoptin SR) verapamil (Coer, Covera HS, Verelan PM)	180-420 120-540 80-320 120-480 120-360	1 1 2 1-2 1
CCBs—Dihydropyridines	amlodipine (Norvasc) felodipine (Plendil) isradipine (Dynacirc CR) nicardipine sustained release (Cardene SR) nifedipine long-acting (Adalat CC, Procardia XL) nisoldipine (Sular)	2.5-10 2.5-20 2.5-10 60-120 30-60 10-40	1 1 2 2 1 1
Alpha-1 blockers	doxazosin (Cardura) prazosin (Minipress) terazosin (Hytrin)	1-16 2-20 1-20	1 2-3 1-2
Central alpha-2 agonists and other centrally acting drugs	clonidine (Catapres) clonidine patch (Catapres-TTS) methyldopa (Aldomet) reserpine (generic) guanfacine (Tenex)	0.1-0.8 0.1-0.3 250-1,000 0.1-0.25 0.5-2	2 1 wkly 2 1 1
Direct vasodilators	hydralazine (Apresoline) minoxidil (Loniten)	25-100 2.5-80	2 1-2