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Rashi Bandey
Apollo College of Pharmacy, Anjora, Durg, Chhattisgarh, India

Hari Prasad Sonwani
Apollo College of Pharmacy, Anjora, Durg, Chhattisgarh, India

Corresponding Author:
Rashi Bandey
Apollo College of Pharmacy, Anjora, Durg, Chhattisgarh, India

Medication regimens against hypertension utilized in the systolic blood pressure intervention study

Rashi Bandey and Hari Prasad Sonwani

Abstract
Objective: Determine the distribution and longitudinal changes in antihypertensive medication regimens in the Systolic Blood Pressure Intervention Trial (SPRINT).
Methods: We used antihypertensive medication data collected by pill bottle review at each visit to categorize antihypertensive regimens by medication class. Free text string variables of medication names were independently reviewed by two clinical pharmacists to create standardized generic medication names and classes.
Results: Figure 1 illustrates longitudinal changes in class combinations and number of drugs at the randomization, 6, 12, and 18-month visits. Fifty-six percent of participants modified their initial regimen by the 6-month visits; 43% of participants made additional modifications to their regimens from the 6-month to the 18-month visit. The most common initial regimens, and least likely regimens to be changed over time, were combinations with an ACEI/ARB and diuretics ± other classes (42% of initial regimens). Participants in the intensive arm added a mean (standard deviation) of 0.6 (0.9) medications to their initial regimens in the first 18-months compared to -0.1 (0.9) in the standard arm.
Conclusion: Intensive blood pressure treatment requires more medication complexity in terms of class and dose. Further study of distinct regimens may reveal if certain class and dose combinations provide better SBP control, safety, or patient satisfaction.

Keywords: Angiotensin II receptor antagonist, Angiotensin-converting enzyme inhibitor, Betablocker, Calcium channel blocker, diuretic

Introduction
Successful treatment of hypertension is possible with limited side effects given the availability of multiple antihypertensive drug classes. The translation of pharmacological research to the treatment of hypertension has been a continuous process, starting with drugs discovered 60 years ago, such as thiazide diuretics (1958) and currently finishing with the newest antihypertensive agent available on the market, the orally active direct renin-inhibitor aliskiren, discovered more than 10 years ago (2000). In between, there has been a continuous rate of discovery, including spironolactone (1957), beta-blockers (Propranolol, 1973), centrally acting alpha-2 adrenergic receptor agonists (Clonidine, 1970s), alpha1-adrenergic receptor blocker (Prazosin, 1975), angiotensin converting enzyme inhibitors (captopril, 1977), calcium channel blockers (Verapamil, 1977), and angiotensin II receptor blockers (Losartan, 1993).
The aim of this review is to describe the various pharmacological classes of antihypertensive drugs, under two major aspects: their mechanisms of action and side effects. The mechanism of action is analysed through a pharmacological approach, i.e. the molecular receptor targets, the various sites along the arterial system, and the extra-arterial sites of action, in order to better understand in which type of hypertension a given pharmacological class of antihypertensive drug is most indicated (see other articles of this issue). In addition, side effects are described and explained through their pharmacological mechanisms, in order to better understand their mechanism of occurrence and in which patients drugs are contra-indicated. This review does not address the effectiveness of immunotherapies in large randomized clinical trials and combination therapies, since these are the matters of other articles of the present issue.
There are multiple classes of antihypertensive medications used for the treatment of HTN; the most recommended classes used as first-line for treatment are:

- Thiazide-type diuretics.
- Calcium channel blockers.
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers

(ARBs).

Thiazide Diuretics

Thiazide and thiazide-like diuretics are usually the first-line of treatment for hypertension in JNC8 guidelines, the thiazide diuretics can be used as the first-line treatment for HTN (either alone or in combination with other antihypertensives) in all age groups regardless of race unless the patient has evidence of chronic kidney disease where angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker is indicated.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial ALLHAT study recommended thiazide diuretics as the first line of treatment for hypertension unless there are contraindications.

Treatment with hydrochlorothiazide as a single agent with a dose of 12.5 mg or 25 mg daily showed no evidence of decreasing morbidity or mortality.

Research shows that thiazide-type diuretics (chlorthalidone and indapamide) are superior in preventing cardiovascular disease at a lower cost. Recommendations are to start them as first-line treatment for hypertension. Multiple studies have shown that thiazide-like diuretics (chlorthalidone and indapamide) in hypertension treatment are more potent than hydrochlorothiazide. They are better at decreasing the risk of cardiovascular disease compared to hydrochlorothiazide.

Chlorthalidone is the drug of choice to start as monotherapy for hypertension. Studies show it to be the best diuretic to control blood pressure and prevent mortality and morbidity. It demonstrated greater effectiveness than hydrochlorothiazide in lowering blood pressure when researchers monitored 24-hour ambulatory blood pressures. Hydrochlorothiazide has a shorter effect during the day in a study that compared the office blood pressure reading with the 24 hours ambulatory blood pressure readings. Switching to chlorthalidone from hydrochloro-thiazide decreases systolic blood pressure by 7 to 8 mm Hg.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that chlorthalidone at 12.5 to 25 mg/day caused fewer cardiovascular complications than amlodipine and lisinopril.

Chlorthalidone is the first choice for older patients with osteoporosis, as it was associated with a lower incidence of pelvic fractures when compared to amlodipine and lisinopril. Compared with doxazosin mesylate and lisinopril, chlorthalidone was better in preventing cardiovascular disease, including strokes and incidence, and when compared with amlodipine, it was better in preventing heart failure.

Calcium Channel Blockers CCBs

Same as thiazide-type diuretics, CCBs are recommended in JNC8 guidelines to be used as a first-line treatment alone or in combination with other antihypertensives in all patients with HTN regardless of age and race, except for patients with chronic kidney disease where ACE inhibitors or ARBs are the recommended first-line treatment.

CCBs have been shown to decrease all cardiovascular events other than heart failure, similar to thiazide diuretics. They can be used as the best alternative to thiazides when patients do not tolerate thiazides.

CCBs divide into two groups: dihydropyridines and non-dihydropyridines

Dihydropyridines are more potent as vasodilators and are used more for HTN treatment. They have less effect on heart contractility and conduction. For this, they are used more for the management of HTN. Nifedipine and amlodipine are the most used medications in this group.

Non-dihydropyridines are less potent as vasodilators and have a better effect on cardiac contractility and conduction. They are used more as antiarrhythmic medications and less for HTN treatment.

For African descent patients, initial treatment for hypertension (without evidence of heart failure or chronic kidney disease) should include CCB or a thiazide diuretic.

Long-acting nifedipine has greater antihypertensive action when compared to amlodipine.

Dihydropyridines should not be a primary treatment for congestive heart failure (CHF) but represent a safe additional treatment in these patients for better blood pressure control or angina pectoris.

Non-dihydropyridines are relatively contraindicated in patients with CHF with reduced ejection fraction, second and third-degree heart blocks, and in patients with sick sinus syndrome.

Compared to valsartan in a study, amlodipine was found to have better control of 24-hour ambulatory blood pressure. In the ASCOT trial, amlodipine was found to be better than atenolol in lowering the risk of cardiovascular disease and is associated with less risk of diabetes development. Compared to thiazide diuretics, amlodipine was equally effective in reducing cardiovascular disease risk regardless of the patient's weight, while thiazides are less effective in normal body mass index (BMI) patients than in patients with obesity.

ACE Inhibitors and ARBs

ACE inhibitors and ARBs are the antihypertensive of choice for patients with heart failure and chronic kidney disease. They are indicated as first-line treatment for patients with chronic kidney disease with evidence of proteinuria. JNC8 guidelines list these two classes of antihypertensive medications as first-line treatment for HTN for non-black patients, along with thiazides and CCBs.

Independent of their antihypertensive effect, they are proven to have a cardio protective effect in patients with a high risk of cardiovascular disease.

Both classes have similar efficacy and share the same indications for treatment; they are both recommended as first-line treatment for patients with left ventricular dysfunction and ST-elevation MI or non-ST elevation MI with the presence of diabetes, systolic dysfunction, or anterior infarct.

Thiazide is better than ACE inhibitors in decreasing blood pressure and preventing stroke; CCBs are better than ACE inhibitors in lowering blood pressure and preventing stroke and heart failure.

Ramipril has been shown to decrease mortality, the incidence of stroke, and MIs when used in patients with symptomatic heart failure or asymptomatic patients with low ejection fraction. The research found perindopril decreases cardiovascular events when used in a patient with stable coronary artery disease and normal systolic dysfunction. Compared with atenolol, losartan was found to be better in reducing morbidity and mortality and better in lowering blood pressure.

Comparing ramipril with telmisartan, they were equivalent in effect in diabetic or heart failure patients, with telmisartan showing a correlation with less angioedema.

Beta-Blockers

Beta-blockers are not indicated as primary treatment for hypertension unless there is a specific indication of heart failure and myocardial infarction.

Beta-blockers are associated with decreased cardiovascular morbidity and mortality when used in younger patients but are less protective in patients older than 65 and were noted to be associated with an increased risk of strokes.

Combination Therapy

When a patient fails a monotherapy for HTN, a combination should merit consideration. Combining two antihypertensive medications should be a therapeutic option for patients with stage 2 hypertension. One study showed the reduction in blood pressure when drugs from two different classes are combined is approximately five times greater than when the dose of one drug dose doubles.

A combination of ARB-diuretic or ACE inhibitor-CBB is superior to the beta-blocker-diuretic combination. The beta-blocker and diuretic combination is associated with a higher incidence of diabetes. Clinicians should use combinations containing beta-blockers when beta-blockers are indicated in patients with heart failure, tachycardia, or post-MI patients. A combination of thiazide with a potassium-sparing diuretic is as effective as CCB monotherapy in HTN management and showed less incidence of hypokalemia when compared to hydrochlorothiazide monotherapy.

Combination formulations of CCB and diuretics are not as common; ARBs or ACE inhibitors-based combinations are preferred when a combination is required; these types of combinations (ACE inhibitors or ARB-based combinations) should be used in patients with CKD.

The combination of benazepril-amlodipine is superior to the benazepril-hydrochlorothiazide combination in decreasing the incidence of cardiovascular events in patients with high risk, and it decreases the progression of nephropathy.

The ACE inhibitor-ARB combination is not recommended; it showed a higher incidence of side effects with no added benefits.

When the combination of 2 medications does not achieve the treatment goal, a third agent should be added, usually done by adding a third agent of the first line group of drugs (thiazide-like diuretics, CCB, ACE inhibitors, and ARBs).

When the patient fails the three-drug regimen, the clinician should consider treatment for resistant HTN, adding a fourth antihypertensive agent from any other classes.

Loop diuretics

Are more effective than thiazides in patients with a low estimated glomerular filtration rate of less than 30 mL/min. They have been approved to treat peripheral edema associated with congestive heart failure and other noncardiac causes of edema, as in liver and kidney diseases. Loop diuretics are not the first-line agents for HTN treatment.

Potassium Sparing Diuretics

Mineralocorticoid receptor antagonists are not usually used as first-line treatment. Spironolactone and eplerenone are considered good in hypertension treatment when added to other antihypertensive medications in resistant HTN; this group of medications is effective when added to triple hypertension medications regimen but should be used cautiously when added to ACE inhibitors or ARBs due to the higher incidence of hyperkalemia. They effectively treat heart failure as they are proven to decrease mortality rates and help decrease hypokalemia rates. Spironolactone is superior to doxazosin and bisoprolol in lowering blood pressure when added to first-line antihypertensive agents in treating resistant hypertension.

Hydralazine

Hydralazine can be added to a regimen to treat resistant hypertension, either alone or in combination with nitrates, in case of heart failure. Hydralazine is associated with increased sympathetic tone and increased sodium avidity; adding a beta-blocker and loop diuretics helps to decrease these effects.

Clonidine

Clonidine is a central alpha-2 agonist; it is not first-line therapy but can be used as an additional agent when the patient fails combination therapy. The transdermal form is preferred.

Minoxidil

Minoxidil is usually an option when the patient fails treatment with hydralazine. It usually provides good blood pressure control, but it is associated with fluid retention, for which adding a loop diuretic is helpful. It increases the sympathetic tone that may require adding a beta-blocker.

Alpha-blockers

Alpha-blockers should not be used to treat hypertension as a first-line agent because they are not as effective in preventing cardiovascular disease compared with other first-line agents.

Mechanism of Action

Thiazide and Thiazide like diuretics

Mechanism of action for thiazide-type diuretics is not fully understood. Thiazides inhibit sodium transport in the distal tubule by blocking the Na/Cl channels. Thiazides can have a small effect on the proximal tube by impairing sodium transport, but the main action is on the distal tubule. Thiazides cause initial volume depletion associated with decreased cardiac output, which recovers within 6 to 8 weeks of starting the treatment in a reverse autoregulation mechanism while the blood pressure remains controlled; thiazide diuretics can acutely activate the renin-angiotensin system and cause systemic vascular resistance, which prevents a good response to the diuretic treatment, this increase in renin-angiotensin activity may resolve with chronic thiazide treatment, the addition of an ACE inhibitor or ARB can enhance the blood pressure control. Also, the thiazide-type diuretics have a modest vasodilation effect, although the mechanism is still unclear.

Calcium channel blockers

The mechanism of action of CCBs is related to the inhibition of Ca^{2+} entry to the cells; this occurs by binding to the L-type voltage-gated calcium channels located in the heart muscle. This effect can cause peripheral vasodilation, which is seen mainly in dihydropyridines, or a negative

inotropic effect on the heart muscle in non-dihydropyridines, inhibiting the sinoatrial and atrioventricular nodes leading to slow cardiac contractility and conduction.

ACE inhibitors
ACE inhibitors decrease the blood pressure by inhibiting the angiotensin-converting enzyme; this causes a decline in the production of angiotensin II and increases the bradykinin level by inhibiting its degeneration, which leads to vasodilation.

ARBs
ARBs work by blocking the binding of angiotensin II to the angiotensin 1 AT1 receptors, which inhibit the angiotensin II effect. In contrast to ACE inhibitors, ARBs do not affect the kinin levels.

Beta-blockers
Beta-blockers work by inhibiting the catecholamines from binding to the Beta 1, 2, and 3 receptors. Beta-1 receptors are found primarily in the heart muscle, beta-2 receptors are located in the bronchial and peripheral vascular smooth muscles, and beta-3 receptors appear in adipose tissue of the heart. Cardio-selective beta-blockers (e.g., metoprolol succinate, metoprolol tartrate, atenolol, betaxolol, and acebutolol) inhibit only beta-1 receptors, causing fewer bronchospasms. By inhibiting the catecholamines binding to the beta receptors, the beta-blockers have a negative inotropic effect, which results in vasodilation of coronary and peripheral arteries and decreases the heart rate, which helps to reduce the oxygen consumption.

Loop diuretics
Loop diuretics work by increasing the sodium exertion at the level of the medullary and cortical aspects of the thick ascending limb. This action causes a decrease in volume, which leads to decreased blood pressure.

Potassium Sparing Diuretics
Act on the principal cells in the late distal tubule and the collecting duct; they inhibit the sodium reabsorption at this level in association with decreased excretion of potassium and hydrogen ions. Spironolactone and eplerenone are considered mineralocorticoid receptor antagonists, inhibiting the mineralocorticoid receptor.
Hydralazine is an arteriolar vasodilator; it inhibits Ca2+ release in the smooth muscles of the vessels by decreasing its cytoplasmic concentration.

Clonidine
Stimulates alpha-2 receptors located in the rostral ventrolateral medulla, which reduces the sympathetic outflow from the central nervous system and decreases plasma norepinephrine levels leading to decreased cardiac output.

Minoxidil
Is an arteriolar vasodilator; it opens the adenosine triphosphate-sensitive potassium channels located in the smooth muscles of the vessels.

Alpha-blockers
Act by inhibiting alpha-1 receptors, which decrease vascular smooth muscle contractions, leading to vasodilation.

Administration
Thiazide type diuretics are given only as oral forms, Hydrochlorothiazide is available in 12.5 and 25 mg tablets, but the daily dose can be up to 50 mg daily. Chlorthalidone is available in 25 and 50 mg tablets, but the daily dose can be up to 100 mg daily.

Dihydropyridine
Calcium channel blockers are administered orally. Amlodipine's maximum dose is 10 mg daily. Nifedipine's extended-release maximum dose is 120 mg daily. Non-dihydropyridine CCBs are available in oral and intravenous forms; the diltiazem intravenous IV form is useful for heart rate control in cardiac arrhythmias. The maximum oral dose of diltiazem is 480 mg daily. Verapamil is available in oral and IV forms as well. The IV form is used for tachyarrhythmias, especially atrial fibrillation. Oral verapamil dose can be up to a maximum of 480 mg daily.
All ACE inhibitors are given orally; enalapril is the only exception as it has an IV form. On the other hand, all ARBs are only oral dose forms.

Beta-blockers
Are available in oral and IV forms. Loop diuretics are available in oral or IV forms, while potassium-sparing diuretics are used mainly in oral forms.

Hydralazine
Administration can be oral or intravenous. The maximum hydralazine oral dose is 300 mg daily.

Clonidine
Transdermal form is the preferred method of administration as oral forms can increase the risk of rebound hypertension. Transdermal maximum clonidine dose is 0.3 mg weekly, while oral immediate-release form maximum dose is 0.3 mg three times daily.

Minoxidil
Is given orally for hypertension treatment. Alpha-blockers are available only orally for hypertension treatment.

Adverse Effects
Thiazides Side Effects
Thiazide and thiazide-like diuretics are associated with multiple side effects. Most of these side effects are directly related to the diuretic dose; hypokalemia and hyponatremia are the most common metabolic effects, followed by hyperuricemia, hypomagnesemia, hyperlipidemia, and increased glucose levels.
Chlorthalidone was found in a study to have an increased risk of hospitalization due to severe hypokalemia in the elderly. Other non-dose-related side effects are sexual dysfunction and sleep disturbance.

CCB Side Effects
The treatment with dihydropyridine CCBs is often associated with peripheral edema. Long-acting nifedipine is associated with a higher incidence of edema when compared to amlodipine; the edema is related to the dose of the CCB. It is not related to sodium or fluid retention or developing

heart failure. Since CCBs induced edema is not a result of volume increase, it does not improve with diuretics therapy; on the other hand, the combination of CCBs with ACE inhibitors or ARBs to a lesser effect showed decreased risk of developing peripheral edema. Dihydropyridines can cause lightheadedness, flushing, headaches, and gingival hyperplasia.

Non-dihydropyridines are associated with bradycardia and can cause constipation in 25% of patients.

CCBs inhibit platelet aggregation and are associated with an increased risk of gastrointestinal bleeding; caution is necessary when prescribing these agents to older patients and patients with a high risk of bleeding.

ACE Is and ARBs Side Effects

The most common side effects related to ACE inhibitors are cough, hypotension, fatigue, and azotemia; reversible renal impairment is a common side effect, especially if the patient develops volume depletion due to diarrhea or vomiting.

Cough can occur in up to 20% of patients on ACE inhibitors. It takes up to 14 to 28 days after discontinuation for the cough to resolve. The incidence of cough is less common with ARB treatment; comparing losartan with hydrochlorothiazide showed a similar incidence of cough in both medications. ARBs are safe to use in asthma patients; candesartan did not correlate with an increase in the incidence of cough in patients with asthma compared to CCBs. Ramipril demonstrated a higher rate of cough incidence compared to telmisartan.

ACE inhibitor treatment is commonly associated with mild hyperkalemia. Even in patients with normal renal function, the risk of hyperkalemia increases in patients with renal failure, diabetes, or CHF. Ramipril and telmisartan are similar in rates of developing hyperkalemia, acute kidney injury, and syncope. But telmisartan is associated with more incidence of symptomatic hypotension.

Angioedema is a rare side effect of ACE inhibitors; it appears in 0.3% of patients on ramipril; ARBs are less associated with angioedema than ACE inhibitors.

In Black patients, ARBs correlated with less incidence of both cough and angioedema.

Beta-blockers

Common side effects of beta-blockers are bradycardia, constipation, depression, fatigue, and sexual dysfunction. Additionally, they are associated with bronchospasm and worsening symptoms of peripheral vascular disease. They can cause a flare-up of Raynaud syndrome.

Loop diuretics

Are associated with electrolyte imbalance, mainly hypokalemia, hyponatremia, hypomagnesemia, and hypochloremia. Other metabolic adverse reactions are dehydration, hyperuricemia, and hyperlipidemia. Ototoxicity and deafness may occur with loop diuretics treatment.

Side effects of the Mineralocorticoid receptor antagonists

Hyperkalemia is the major side effect of this group of medications. They can cause metabolic acidosis due to decreased exertion of hydrogen ions. Erectile dysfunction and gynecomastia in men and irregular menstrual periods in women can also occur.

Hydralazine

Can cause headaches, flushing, palpitations, dizziness, hypotension symptoms, and dizziness due to the sympathetic system stimulation. It is associated with drug-induced lupus erythematosus, hemolytic anemia, and other immune phenomena.

Clonidine's

Common side effects are drowsiness, headache, dizziness, irritability, nausea and vomiting, constipation, upper abdominal pain, and bradycardia, but other serious side effects can occur as angioedema, atrioventricular block, and severe hypotension.

Minoxidil

Is associated with hirsutism.

Alpha-blockers

Are associated with tachycardia and orthostatic hypotension as a result of venous dilation

Contraindications

Thiazide

Type diuretics are contraindicated if the patient is anuric, and in patients with sulfonamide allergies.

CCBs are contraindicated in patients with hypersensitivity to the drug. Non-dihydropyridines contraindications are patients with heart failure with reduced ejection fraction, patients with sick sinus syndrome, and patients with second or third-degree AV blockade. Dihydropyridine should be avoided in cardiogenic shock patients, severe aortic stenosis, and unstable angina; special caution is necessary when dihydropyridine is useful in hepatic impaired patients.

ACE inhibitors

Are contraindicated in patients with a history of previous hypersensitivity to ACE inhibitors, history of ACE inhibitor-related angioedema, other types of angioedema, pregnancy, or the use of aliskiren. Relative contraindications are patients with volume depletion, abnormal renal function, and patients with aortic valve stenosis. ARBs are contraindicated in pregnancy. A combination of ACE inhibitors and ARBs is relatively contraindicated. Other relative contraindications for ARB treatment include patients with volume depletion, patients on other medications that cause hyperkalemia, or patients with abnormal renal function

Beta-blockers

Are contraindicated in asthma patients, especially nonselective beta-blockers. Relative contraindications are hypotension and bradycardia. They should be avoided in patients with cocaine-induced coronary artery spasms

Loop diuretics

Are contraindicated in patients with hypersensitivity to sulfonamides, anuric patients, and patients with hepatic coma

Potassium-sparing diuretics

Are contraindicated in patients with chronic kidney disease, hyperkalemia, and caution is necessary when combining them with ACE inhibitors, ARBs, and aliskiren. They are

contraindicated in patients with hypersensitivity to this class.

Clonidine
Is contraindicated in patients with hypersensitivity to alpha-2 agonists and should be avoided in patients with depression and recent myocardial infarctions.

Hydralazine
Is contraindicated if the patient has a history of hydralazine allergy. In patients with coronary artery disease, hydralazine can stimulate the sympathetic system. In patients with rheumatic mitral valve disease, pulmonary artery pressure can increase due to hydralazine treatment.

Minoxidil
Is contraindicated in pregnant and breastfeeding females and patients with hypersensitivity to minoxidil.
Contraindications to alpha-blockers include patients with a history of orthostatic hypotension and patients on phosphodiesterase inhibitors.

Conclusion
Choice of antihypertensive agent(s) is a clinical decision based on many factors, including an individual patient's BP, BP goal, and risk conditions such as HF, prior MI, classic angina, and edema. Consideration should be given not only to the benefits of BP lowering which are well established and not in dispute, but also to the metabolic risks of some BP lowering drugs. There are clear cardiovascular outcome benefits as a result of BP lowering. It is less clear what the impact of new onset diabetes is with regard to long term macrovascular complications. However, as the prevalence of hypertension in those at risk for diabetes increases, it is important to bear in mind the metabolic consequences of antihypertensive medications. If thiazide diuretics and/or β blockers are agents of choice based on an individual patient's clinical characteristics, then the lowest possible dose and close monitoring should be employed in order to recognize and manage metabolic adverse outcomes early on, while still maintaining adequate BP control.

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