Review On Anti-Hypertensive Agents

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Abstract
In this review the discussion was about the prevalence, awareness, diagnosis, treatment, and control of hypertension in a population-representative sample of adults. Hypertension is a major health problem throughout the world because of its high prevalence and its association with increased risk of cardiovascular disease. Advances in the diagnosis and treatment of hypertension have played a major role in recent dramatic declines in coronary heart disease and stroke mortality in industrialized countries. However, in many of these countries, the control rates for high blood pressure have actually slowed in the last few years. This activity discusses the guidelines for selecting the appropriate antihypertensive medications.

Keywords: hypertension, antihypertensive agent, treatment of hypertension, cardiovascular disease.

INTRODUCTION

Hypertension, or high blood pressure, is a medical condition characterized by consistent elevated blood pressure levels, measured as systolic/diastolic pressure. It is often defined as readings equal to or exceeding 130/80 mmHg. Uncontrolled hypertension can lead to severe health complications, including cardiovascular issues and kidney damage. High blood pressure (hypertension) is one of the most important preventable causes of premature morbidity and mortality in the UK. Hypertension is a major risk factor for ischemic and hemorrhagic stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline and premature death.

HISTORY OF HYPERTENSION

The modern history of hypertension begins with the understand the cardio vascular system with the work of physician William Harvey (1578–1657), who described the circulation of blood in his book "De motu cordis. The English clergyman Stephen Hales made the first published measurement of blood pressure in1733. Descriptions of hypertension as a disease came among others from Thomas Young in 1808 and especially Richard Brightin1836.

CLASSIFICATION OF HYPERTENSION

There are two main types:

Essential (primary) hypertension

1. The main form of high blood pressure–accounts for around90–95% of cases
2. Has no single identifiable cause Potential cause include genetic and environmental factor

Secondary hypertension

Rare forms of high blood pressure

1. Caused by another medical conditioner treatment
2. Cause includes kidney problems (Reno vascular hypertension), an adrenal gland tumors, and thyroid disease.

Other types of high blood pressure include:

1. Isolated systolic hypertension–the systolic pressure (top number) is raised but the diastolic pressure is normal
2. Isolated diastolic hypertension–the diastolic pressure (bottom number) is raised but the systolic pressure is normal
3. White coat hypertension–where the blood pressure is raised due to the stress of a visit to the doctor or nurse.

PATHOPHYSIOLOGY

Objectives

1. Understand the hemo dynamic determinants of systemic hypertension.
2. Recognize primary and secondary forms of hypertension.
3. Understand the role of the kidney in systemic hypertension
4. Recognize the role of Angiotensin-II, Aldo-sterone, and the sympathetic nervous system in the pathogenesis of

hypertension.
Hypertension is a chronic elevation of blood pressure that, in the long-term, causes end-organ damage and results in increased morbidity and mortality. Blood pressure is the product of cardiac output and systemic vascular resistance vascular tone may be elevated because of increased α-adreno- receptor stimulation or increased release of peptides such as Angiotensin.

Diagnosis

Hypertension is diagnosed on the basis of persistently high blood pressure. Traditionally, this requires three separate sphygmomanometer measurements at one monthly interval.

Equipment

ECG

The ECG may provide suggestive or supportive evidence of Hypertension by demonstrating right ventricular hypertrophy and strain, and right atrial dilation. Right ventricular hypertrophy on ECG is present in 87% and right axis deviation in 79% of patients with hypertension. However, the ECG has in adequate sensitivity (55%) and specificity (70%) to be a screening tool for detecting significant hypertension. A normal ECG does not exclude the presence of severe PH.

Sphygmomanometer

A sphygmomanometer has three parts:

- a cuff that can be inflated with air,
- a pressure meter (manometer) for measuring air pressure in the cuff, and
- a stethoscope for listening to the sound the blood makes as it flows through the brachial artery (the major artery found in your upper arm).

The scale of the pressure meter ranges from 0 to 300 mmHg. The pressure meter has a rubber pump on it for inflating the cuff and a button for letting the air out.
To measure blood pressure, the cuff is placed around the bare and stretched out upper arm, and inflated until no blood can flow through the brachial artery. Then the air is slowly let out of the cuff.
As soon as the air pressure in the cuff falls below the systolic blood pressure in the brachial artery, blood will start to flow through the arm once again. This creates a pounding sound when the arteries close again and the walls of the vessels hit each other after a heart beat. The sound can be heard by placing the stethoscope close to the elbow. Right when you start to hear this pounding for the first time you can read your systolic blood pressure off the pressure meter.
The pounding sound stops when the air pressure in the cuff falls below the diastolic blood pressure in the brachial artery. Then the blood vessels remain open. Right when the pounding stops, you can read the diastolic blood pressure off the pressure meter.

Chest radiograph

A **chest radiograph**, called a **chest X-ray** (**CXR**), or **chest film**, is a projection radiograph of the chest used to diagnose conditions affecting the chest, its contents, and nearby structures. Chest radiographs are the most common film taken in medicine.

Transthoracic Doppler-echocardiography

Transthoracic Doppler-echocardiography (TTE) is an excellent non-invasive screening test for the patient with suspected pulmonary hypertension. A transthoracic echocardiogram (TTE) is the most common type of echocardiogram, which is a still or moving image of the internal parts of the heart using ultrasound. In this case, the probe (or ultrasonic transducer) is placed on the chest or abdomen of the subject to get various views of the heart. It is used as a non-invasive assessment of the overall health of the heart, including a patient's heart valves and degree of heart muscle contraction (an indicator of the ejection fraction). The images are displayed on a monitor for real-time viewing and then recorded.

Drug used in hypertension

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 antihypertensive) 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 pressure. Hydrochlorothiazide has a shorter effect during the day in a study that compared the office blood pressure reading with the 24-hour ambulatory blood pressure readings. Switching to chlorthalidone from hydrochlorothiazide 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 antihypertensive 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.

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 auto regulation 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 Ca2+ 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 decrease 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 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 work by inhibiting the catecholamine's 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 the 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 catecholamine's binding to the beta receptors, the beta-blockers have a negative inotropic effect, which results in a decrease in the heart rate, which helps to reduce oxygen consumption.

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 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 in the vessels' smooth muscles.

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.
Dihydropyridines 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-dihydropyridines 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. The maximum transdermal clonidine dose is 0.3 mg weekly, while the 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; hypokalaemia and hypernatremia are the most common metabolic effects, followed by Hyperuricemia, hypomagnesaemia, hyperlipidaemia, and increased glucose levels.
Chlorthalidone was found in a study to have an increased risk of hospitalization due to severe hypokalaemia in older people. Other non-dose-related side effects are sexual dysfunction and sleep disturbance.

CCB Side Effects

The treatment with dihydropyridines 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 CCB-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 a decreased risk of developing peripheral edema. Dihydropyridines can cause light-headedness, 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 azotaemia; reversible renal impairment is a common side effect, especially if the patient develops volume depletion due to diarrhoea 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 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 hyperkalaemia. Even in patients with normal renal function, the risk of hyperkalaemia increases in patients with renal failure, diabetes, or CHF. Ramipril and telmisartan are similar in rates of developing hyperkalaemia, acute kidney injury, and syncope. 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 fewer incidences 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, hypomagnesaemia, and hypochloremia. Other metabolic adverse reactions are dehydration, Hyperuricemia, and hyperlipidaemia. Ototoxicity and deafness may occur with loop diuretics treatment.

Side effects of the Mineralocorticoid receptor antagonists: Hyperkalaemia 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 sympathetic system stimulation. It is associated with drug-induced lupus erythematous, haemolytic anaemia, 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 auric, and in patients with sulphonamide allergies.
CCBs are contraindicated in patients with hypersensitivity to the drug. Non-dihydropyridines contraindications include patients with heart failure, reduced ejection fraction, sick sinus syndrome, and second or third-degree AV blockade. Dihydropyridines should be avoided in cardiogenic shock patients, severe aortic stenosis, and unstable angina; special caution is necessary when dihydropyridines is useful in hepatic impaired patients.
ACE inhibitors are contraindicated in patients with a history of previous hypersensitivity to ACE inhibitors, a history of ACE inhibitor-related angioedema, other types of angioedema, pregnancy, or the use of aliskiren. Relative contraindications include patients with volume depletion, abnormal renal function, and 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 hyperkalaemia, or patients with abnormal renal function.
Beta-blockers are contraindicated in patients with asthma, especially no selective beta-blockers. Relative contraindications are hypotension and bradycardia. Some feel they should be avoided in patients with cocaine-induced coronary artery spasms.
Loop diuretics are contraindicated in patients with hypersensitivity to sulphonamides, auric patients, and patients with hepatic coma.
Potassium-sparing diuretics are contraindicated in patients with chronic kidney disease or hyperkalaemia; 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.

Discussion
Hypertension is prevalent worldwide and aging of the population means that there are more and more people with hypertension. Therefore, the scale of the problem of diagnosing, treating and controlling hypertension is immense. Current efforts are channeled towards the detection and treatment of hypertension in middle and old age. The linear rise in the prevalence of hypertension with age means that measures to prevent hypertension, such as a healthy diet and regular physical activity, should start early in life. For these who have already developed hypertension, early diagnosis and treatment is important. Existing antihypertensive drugs are not ideal individually and so a combination of drugs is needed in a large proportion of patients. The choice of such drugs should be rational and evidence-based.

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