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"A Review on Pharmacotherapy of Hypertension"

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ABSTRACT

Hypertension is the most common modifiable risk factor for death and disability including stroke, accelerated coronary and systemic atherosclerosis, heart failure, chronic kidney disease, lowering the BP with antihypertensive drugs, and reducing the target organ damage and prevalence of the occurrence of cardiovascular disease.

According to the 2017 American college of cardiology (ACC)/American heart association (AHA) hypertension guidelines hypertension is defined as systolic BP is ≥130 mmHg or diastolic BP is ≥80 mmHg.

BP should be lower than 130/80 mmHg in patient with CHD, CHF, after renal transplantation, diabetes mellitus and stroke.

The initial antihypertensive agent should be generally selected from one of the following four classes—thiazide diuretics, ACE inhibitors, ARBs, and calcium channel blockers, shown to reduce cardiovascular events.

There are two interventional approaches—Renal Denervation and Baroreflex activation therapy, which are used in clinical practice for treatment of several treatment resistant hypertensions. Other interventional approaches are carotid body ablation and AVF placement but none of them prevent cardiovascular disease outcome or death in hypertensive patient.

Keywords: Target Blood Pressure, Antihypertensive Drugs Therapy, Renal Denervation, Carotid Body Ablation Therapy

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I. INTRODUCTION

High blood pressure, termed "hypertension," is a condition that afflicts more than 50 million Americans and is a leading cause of morbidity and mortality. Hypertension is much more than a "cardiovascular disease" because it affects other organ systems of the body such as kidney, brain, and eye. Tens of millions of Americans are not even aware of being hypertensive because it is usually asymptomatic until the damaging effects of hypertension (such as stroke, myocardial infarction, renal dysfunction, etc.) are observed. Hypertension is the elevation of systolic BP, diastolic BP, or both above normal levels, is common in developed and developing countries and increases in prevalence with age increase. Although in recent years

hypertension has been defined as a BP of 140/90 mmHg or more, the 2017 American College of Cardiology-American Heart Association (ACC-AHA) Hypertension Guideline adopted a lower threshold, in which hypertension is defined as a systolic BP of 130 mmHg or more or a diastolic BP of 80 mmHg or more [1] . Among adults in the United States, the overall prevalence of hypertension was 31.9% under the previous definition (blood pressure, ≥140/90 mmHg) and is 45.6% according to the 2017 ACC/AHA guideline definition (BP ≥ 130/80 mmHg) . Similarly, the rate of hypertension control was 61.0% among those receiving treatment at a target of less than 140/90 mmHg but only 46.6% at a target of less than 130/80 mmHg

Worldwide, hypertension is the leading modifiable and major risk factor for CV events and mortality in adult. Hypertension is present in 69% of adults with a first MI [2] , in 77% of adults with a first stroke , in 74% of adults with HF , and in 60% of older adults with PAD . Hypertension is also a major risk factor for development of SCD, a dissecting aortic aneurysm, angina pectoris, LVH, thoracic and abdominal aortic aneurysms, CKD, atrial fibrillation, DM, vascular dementia and

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ophthalmologic disease . The increased risk associated with BP elevation can be greatly reduced by treatment with antihypertensive drugs that lower both BP and related target organ damage. A total of 69 drugs in 15 different classes, many of which are also available in single pill combinations, have been approved for the treatment of hypertension in the United States. Despite this treatment options, an estimated 10% to 15% of the general RH, is defined as uncontrolled BP on ≥3 antihypertensive drugs of different classes, in which one of them is diuretic, at optimal doses or requiring ≥4 drug to control blood pressureand causes of RH are primarily hyperaldosteronism, Renovascular disease, Cushing syndrome and Pheochromocytoma. In addition, ≈0.5% of hypertensive patients have refractory hypertension, defined as uncontrolled BP on ≥5 drugs. Recent drug monitoring studies have revealed no adherence to BP lowering therapy in 25% to 65% of patients with apparent TRH

II. DEFINITION

Hypertension is high blood pressure. Blood pressure is the force of blood pushing against the walls of arteries as it flows through them. Arteries are the blood vessels that carry oxygenated blood from the heart to the body's tissues.

III. DESCRIPTION

Blood flows through arteries it pushes against the inside of the artery walls. The more pressure the blood exerts on the artery walls, the higher the blood pressure will be. The size of small arteries also affects the blood pressure. When the muscular walls of arteries are relaxed, or dilated, the pressure of the blood flowing through them is lower than when the artery walls narrow, or constrict.

❖ Blood pressure is highest when the heart beats to push blood out into the arteries. When the heart relaxes to fill with blood again, the pressure is at its lowest point. Blood pressure when the heart beats is called systolic pressure. Blood pressure when the heart is at rest is called diastolic pressure.When blood pressure is measured, the systolic, pressure is stated first and the diastolic pressure second. Blood pressure is measured in millimeters of mercury (mm Hg). For example, if a person's systolic pressure is 120 and diastolic pressure is 80, it is written as 120/80 mm Hg. The American Heart Association considers blood pressure less than 140 over 90 normal for adults.

❖ Hypertension is a major health problem, especially because it has no symptoms. Many people have hypertension without knowing it, in the United states, about 50 million people age six and older have high blood pressure. Hypertension is more common in men than women and in people over the age of 65 than in younger persons. More than half of all Americans over the age of 65 have hypertension. It is also more common in African-Americans than in white Americans.

❖ Hypertension is serious because people with the condition have a higher risk for heart disease and other medical problems than people with normal blood pressure. Serious complications can be avoided by getting regular blood pressure checks and treating hypertension as soon as it is diagnosed.

C

If left untreated, hypertension can lead to the following medical conditions;

- Arteriosclerosis, also called **atherosclerosis**
- Heart attack
- Stroke
- Enlarged heart
- Kidney damage

IV. CLASSIFICATION

Table 1 : Classification of Hypertension

Category	Systolic BP[a] (mm Hg)		Diastolic BP[a] (mm Hg)
Normal	<120	and	<80
Pre-hypertension	120-139	or	80-89
Stage 1 hypertension	140-159	or	90-99
Stage 2 hypertension	≥ 160	or	≥ 100

[a]BP = Blood pressure

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Table 2: Classification of Hypertension According to WHO/ISH*

Category	Systolic BP[a] (mm Hg)	Diastolic BP[a] (mm Hg)
Optimal	< 120	< 80
Normal	< 130	< 85
High Normal	130-139	85-89
Grade I (mild hypertension)	140-159	90-99
Sub group: borderline	140-149	90-94
Grade 2 (moderate hypertension)	160-179	100-109
Grade 3 (severe hypertension)	≥ 180	≥ 110
Isolated Systolic Hypertension (ISH)	≥ 140	< 90
Subgroup (borderline)	140-149	< 90

ISH = International Society of Hypertension

Secondary Hypertension

A) Systolic hypertension with wide pulse pressure:

Aortic regurgitation
Thyrotoxicosis
Patent ductus arteriosus

B) Systolic and diastolic hypertension with increased PVR

1. Renal
   - Glomerulonephritis (acute or chronic)
   - Pyelonephritis
   - Polycystic kidneys
   - Renal artery stenosis

2. Endocrine
   - Cushing's syndrome (excessive glucocorticoids)
   - Congential adrenal hyperplasia
   - Conn's syndrome (primary hyperaldosteronism)
   - Phaeochromocytoma
   - Hypothyroidism
   - Acromegaly

3. Neurogenic
   - Raised intracranial pressure
   - Psychological ("white coat hypertension")
   - Acute porphyria
   - Lead poisoning

4. Miscellaneous

Coarctation of the aorta
Polyarteritis Nodosa
Hypercalcaemia
Increased intravascular volume (PRV)

T1able 3. Common causes of secondary hypertension [3] .

Following are the basic investigation of hypertension:

- Complete blood count-TLC, DLC, Hb %, RBC
- Renal function test-Blood urea, serum creatinine, potassium, Sodium, calcium, uric acid
- Blood sugar level
- Urinalysis
- Lipid profile
- Thyroid function test
- Electrocardiography
- Urine albumin to creatinine ratio
- Measure plasma aldosterone/Renin ratio
- Measurement of 24 hours urinary metanephrines.

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Table 3. Basic investigation of hypertension .The aldosterone/renin ratio is effective screening test for primary aldosteronism . Collection of urine of 24 hours during ingestion of the patient normal diet can be helpful in estimating dietary sodium and potassium intake, calculating creatinine clearance and measuring aldosterone excretion. Measurement of 24 hours urinary metanephrines or plasma metanephrines is an effective screen for patients in whom Pheochromocytoma is suspected . Imaging for renal artery stenosis should be reserved for patient in whom there is an increased level of suspicion. Regarding target organ damage, 24 hour urinary albumin excretion and left ventricular mass index are increased in resistant hypertension .

Method of Measuring Hypertension

Palpatory Method
Ausculatory Method (Instrument : Sphigmomanometre)

RISK FACTORS

High Blood pressure has many risk factors. Some you can't control.

Age
Family history
Tobacco use
Sodium intake
Low potassium intake
Excessive alcohol

V. CLINICAL MANIFESTATIONS

The manifestations of hypertensive crises are those of end-organ dysfunction:

1. Hypertensive encephalopathy
2. Acute aortic dissection
3. Acute myocardial infarction
4. Acute cerebral vascular accident
5. Acute hypertensive renal injury

It is important to recognize that the absolute level of BP may not be as important as the rate of increase. Patients with longstanding hypertension may tolerate systolic BPs of 200 mm Hg or diastolic BPs of up to 150 mm Hg without developing hypertensive encephalopathy, while children or pregnant women may develop encephalopathy with diastolic BPs 100 mm Hg.

VI. TREATMENT OF HYPERTENSION

The treatment of hypertension consists of both nonpharmacologic and pharmacological approaches. Treatment decision depends on whether there is pre-existing CV, DM, and CKD. For patient with stage one hypertension and without these conditions, the 2017 AHA/ACC guideline recommended calculation of 10 years risk of cardiovascular disease. If the risk is less than 10%, it is reasonable to implementation life style modification alone for 3 - 6 month. For stage 2 hypertension with pre-existing like DM, CKD and 10 years risk of CV event is 10% or high both life style modification and medication is recommended.

1. Nonpharmacological Treatment

Following are the nonpharmacologic way to treatment of hypertensions.

- **Weight Loss**
- **Dietary Salt Restriction**
- **Physical Activity**
- **Moderate Alcohol Intake**
- **High Fiber and Low fat Diet**
- **Withdrawal of Interfering Medicatio**ns

Pharmacological Treatment

DRUG USED IN THE TREATMENT OF HYPERTENSION

- The 2017 ACC/AHA guideline recommended initiation of anti hypertensive drug treatment with two first line drug from different classes, either as separate agent or in fixed dose combination and target BP should be less than 130/80 mmHg[1].

Initial drug selection:

- The initial agent can be selected from one of the following four classes: Angiotensin converting enzyme inhibitors (ACE inhibitors), Angiotensin receptors blockers (ARBs), Calcium channel blockers (CCBs) and thiazide type of diuretics and each class of antihypertensive drugs reduces CV events.
- A meta-analysis of 147 randomized controlled trials of 464,000 patients with hypertension demonstrated that except for major effect of beta blockers administered after MI reduced CAD event and calcium channel blockers reduced stroke—all major antihypertensive drug class (Diuretic, Angiotensin converting enzyme inhibitors, Angiotensin receptors blockers, beta blockers and calcium channel blockers) causes reduction in CAD event and stroke for

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reduction in BP. The 2011 ACC/AHA hypertension guideline state that choice of antihypertensive drugs in the treatment of adult hypertension depend on efficacy, tolerability, presence of specific comorbities and cost [4] .

Following are the medicines during treatment of hypertension:
· Non steroidal anti-inflammatory drugs
· Oral contraceptives pills
· Corticosteroids
· Tricycle antidepressant drugs
· Monoamine oxidase inhibitors

Table 4. Medicines avoided during treatment of hypertension .

- The 2011 ACC/AHA hypertension guidelines recommended that elderly patient with primary hypertension may be treated with Diuretics, ACE inhibitors, ARBs, Beta blockers, and calcium channel blockers (CCBs)

❖ The 2013 JNC 8 guidelines for management of hypertension recommended that non black adult with primary hypertension is treated with diuretics, Angiotensin converting enzyme inhibitors, Angiotensin receptors blockers and calcium channel blockers

❖ The 2014 American society of hypertension (ASH)/International society of hypertension (ISH) guideline recommended that non black adult with primary hypertension aged <60 years should be treated with Angiotensin converting enzyme inhibitors(ACE inhibitors) or Angiotensin receptors blockers (ARBs). These guidelines recommended that non black adult with age ≥ 60 years with primary hypertension is treated with diuretics, CCBs, ACE inhibitors or ARBs.These guidelines also recommended that black adult with primary hypertension is treated calcium channel blockers or thiazide diuretics [5]

❖ The 2017 American college of cardiology (ACC)/American heart association (AHA) hypertension guidelines a regarding antihypertensive drug treatment for primary hypertension and secondary hypertension as follow

1. White and Their Non Blacks Aged <60 Years with Primary Hypertension

❖ The first choice of antihypertensive drug should be ACE inhibitors or ARBs and second choice is diuretic or calcium channel blockers and if third drug is needed then combination of ACE inhibitors or ARBs plus thiazide diuretic plus calcium channel blockers is given.

❖ **2. White and Other Non Blacks Aged ≥60 Years with Primary Hypertension**

The first choice of antihypertensive drug should be thiazide diuretics or CCBs and second choice is ACE inhibitors or ARBs and if third antihypertensive is needed then combination of thiazide diuretic plus CCB plus ACE inhibitors OR ARB] .

❖ **3. Blacks with Primary Hypertension**

The first antihypertensive drug should be thiazide diuretic or CCBs and if third antihypertensive is needed then combination of thiazide diuretic plus CCBs plus ACE inhibitors or ARB should be given]

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❖ **4. Stable Coronary Heart Disease with Hypertension**

Patient with stable CAD and hypertension is treated with beta blockers plus ACEs inhibitors or ARBs and if third antihypertensive drug is necessary then combination of beta blockers plus ACE inhibitors or ARB plus thiazide diuretics or CCBs should be administered.

❖ **5. Heart Failure with Reduced Left Ventricular Ejection Fraction and Hypertension**

Patient with HF with reduced left ventricular ejection fraction and hypertension is treated with beta blockers (carvedilol, metoprolol, bisoprolol) plus ACEs inhibitors or ARBs plus diuretics] .

❖ **6. Heart Failure with Preserved Left Ventricular Ejection Fraction**

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Patient with HF and preserved left ventricular ejection fraction with hypertension should have volume over load so treated with diuretics and hypertension is treated with beta blockers plus ACEs inhibitors or ARSs plus mineralocorticoid receptors antagonist] .

❖ **7. Chronic Kidney Disease with Heart Failure**

Patient with hypertension and CKD stage-3 or higher or stage-1 or stage-2 with albuminuria ≥ 300 mg/day should be treated with ACEs inhibitors to slow progression of CKD . If patients don't tolerate ACEs inhibitors, patients should be treated with ARBs [1] . Adult with stage 1 or 2 CKD without Albuminuria should be treated with first line antihypertensive drug [1] . If three antihypertensive needed then gives ACE inhibitors or ARB plus thiazide diuretic plus CCBs. After kidney transplantation, hypertension is treated with CCBs to improve glomerular filtration rate and kidney survival.

❖ **8. Stroke or Transient Ischemic Attack with Hypertension**

Hypertensive patient with stroke or Transient ischemic attack should be treated with thiazide diuretic or ACEs inhibitors or ARBs . If third antihypertensive drug is needed then give thiazide diuretic plus ACE inhibitors or ARBs plus CCB should added.

9. Peripheral Arterial Disease and Hypertension

Patient with PAD and hypertension should be treated with any of the first line antihypertensive drug that is Diuretics, ACEs inhibitors, ARBs, CCBs and beta blockers similar to patient without peripheral arterial disease .

❖ **10. Hypertension and Diabetes Mellitus**

In patient with hypertension and diabetes mellitus should be treated with ACEs inhibitors or ARBs, CCBs and thiazide diuretic If patients with diabetes mellitus, hypertension and persistent albuminuria, initial treatment with ACEs Inhibitors or ARBs

❖ **11. Thoracic Aortic Aneurysm and Hypertension**

Beta blockers are preferred antihypertensive drug for patient with hypertension and thoracic aortic aneurysm . Beta blockers are also associated with increase improved survival in aortic dissection .

❖ **12. Hypertension and Pregnancy**

Women with hypertension who become pregnant should not treat with ACEs inhibitors, ARBs, direct renin inhibitors or atenolol. Methyldopa, Hydralazine, Nifedipine, and Labetalol is a drug of choice in patient with hypertension and pregnancy.

❖ **13. Resistant Hypertension**

Treatment of RH included detection and treatment of secondary hypertension, use of life style measure and treat obesity and other comorbidities . If fourth antihypertensive drug is required to control blood pressure then give mineral ocorticoids receptors antagonist that is spironolactone in the therapeutic regimen

New Approach for Treatment of Hypertension

1: New Drugs for Treatment of Hypertension

❖ **Antialdosterone Agent**

Aldosterone is a mineralocorticoid that regulates electrolyte and water balance in the body and when aldosterone level elevated in the body can contribute to the development of hypertension and other disease including myocardial hypertrophy fibrosis of myocardium and heart failure .The aldosterone act on mineralocorticoid receptor in the cortical collecting duct of the nephron and mineralocorticoid receptors stimulate expression of sodium channels, resulting in increased sodium and water reabsorption and potassium loss, lead to a volume expanded form of hypertension. Aldosterone is synthesized from 11-deoxycorticosteronein the zonaglomerulosa of adrenal cortex through the action of mitochondrial cytochrome P450 enzyme, aldosterone synthase which is encoded by the CYP11B2 gene

❖ **Mineralocorticoid Receptor Antagonists**

Mineralocorticoid receptor antagonist, Spironolactone monotherapy has modest BP lowering efficacy and recent used as add on therapy in patients with RH. Spironolactone used has been limited due to lack of selectivity for the mineralocorticoid receptor at higher dose because it's structural similarity to progesterone resulting significant progestogenic and antiandrogenicactivity leading to adverse effect in both men and women. The more selective mineralocorticoid receptor antagonist is eplerenone has lack of antiandrogenic effect of spironolactone but it is less potent and short half life (3 - 4 h) lead to reduced antihypertensive efficacy and requirement for twice daily dose. The optimization of MRA activity of dihydropyridine compound led to development of BAY 94 - 886 (finerenone),

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nonsteroidal MRA that has greater selectivity than spironolactone for the MR over other steroid hormone receptors, greater affinity than Eplerenone for MR and no effect on the L-type calcium channel . Finerenone has greater cardiac activity and improve myocardial function without affecting sodium potassium homeostasis in kidney. In preclinical model of hypertension related heart failure and renal dysfunction, finerenone work as greater cardio renal target organ protection than steroidal mineralocorticoid receptor antagonist

❖ **Aldosterone Synthase Inhibitors**

the first orally active aldosterone synthase inhibitors which decrease plasma and urine aldosterone concentration, increase plasma renin activity and prevent the target organ damage in animal models of hypertension and heart failure [, Similar effects on aldosterone and renin level seen in healthy humans and in hypertensive patients. The first randomized double-blind, placebo-controlled trial of LCI699, performed in 524 patients with primary hypertension, compared the efficacy and safety of different doses of LCI699 with eplerenone. All doses of LCI699 produced significant reductions in office systolic BP that were no inferior to those seen with eplerenone. Plasma aldosterone levels were suppressed with LCI699 and increased with eplerenone, both agents were well tolerated.

❖ **Vasopeptidase Inhibitors**

The zinc metalloprotease neprilysin is a therapeutic target for hypertension and other forms of Cardiovascular disease because it degrades the natriuretic peptides atrial natriuretic peptide (ANP), B type natriuretic peptide (BNP), and urodilatin and increase in circulating natriuretic peptide levels that results from neprilysin inhibition leads to natriuresis, vasodilatation, renin-Angiotensin-aldosterone system inhibition, reduced sympathetic drive, and antiproliferative and antihypertrophic effects on heart.

❖ **Dopamine β-Hydroxylase Inhibitor**

Dopamine β-hydroxylase the enzyme that catalyzes the hydroxylation of dopamine to form noradrenaline in the sympathetic nervous system, is a therapeutic target for treatment of hypertension and other cardiovascular disorders characterized by sympathetic activation in HF. Inhibition of Dopamine β-hydroxylase offers theoretical advantages over adrenergic receptor blockade: 1) it causes gradual sympathetic slowdown; 2) it increases dopamine availability, thus causing renal vasodilatation, natriuresis, and diuresis. First, second, and early third generations DβH inhibitors, for example, disulfiram, fusaric acid, and nepicastat, either lacked potency or selectivity for DβH or caused severe CNS-related adverse effects and thus were not clinically useful. Etamicastatis potent and reversible inhibitors of Dopamine β-hydroxylase that not cross the blood brain barriers thus selective for peripheral Dopamine β-hydroxylase when given orally. Studies in healthy men and men with mild to moderate hypertension showed good tolerability and significant dose-dependent decreases in 24-h ambulatory BP

2: Interventional Approach for Treatment of Hypertension

- Renal Denervation
- Baroreflex Activation Therapy
- Carotid Body Ablation
- . Arteriovenous Fistula
- Renal artery Stenting

VII. CONCLUSION

Use lifestyle measure plus BP lowering drugs for secondary prevention of recurrent cardiovascular events in adults with clinical CVD (CHD, CHF and stroke) and an average systolic BP ≥ 130 mmHg or an average diastolic BP ≥ 80 mmHg. The interventional BP lowering treatments performed in patients with TRH, is defined as a SBP > 160 mmHg despite treatment with an average of 5 different antihypertensive drugs. There are two interventional approaches like Renal Denervation and Baroreflex activation therapy, which are most commonly used in clinical practice, and other interventional approaches like AVF, Renal artery Stenting are not used. The BP should be lower than 130/80 mmHg in patients with diabetes mellitus, CHF, CKD, after renal transplantation and for secondary stroke prevention in lacunar stroke. A thiazide diuretics or ACE inhibitors or ARBs is started as a first agent to prescribe, with follow up BP and electrolyte measurement in 3 to 4 weeks. Dose increase or additional medication may be needed. We would recommend regular visits during dose adjustment; combined with home BP measurement, life style factors and medication adherences should be assessed at each visit. Once the BP is <130/80 mmHg, we would recommend follow up at 6-month intervals.

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Abbreviations
BP: Blood pressure.
SBP: Systolic blood pressure.
DBP: Diastolic blood pressure.
AV: Atrioventricular.
ACC: American college of cardiology.
AHA: American heart association.
TLC: Total leukocytes counts.
DLC: Differential leukocytes counts.
HB: Hemoglobin.
RBC: Red blood cells counts.
MRA: Mineralocorticoid receptor antagonist.
MR: Mineralocorticoid receptor.
RDN: Renal denervation.
AVF: Arteriovenous Fistula.
RH: Resistant hypertension.
CVD: Cardiovascular disease.
LVH: Left ventricular hypertrophy.
TIA: Transient Ischemic attack.
SCD: Sudden cardiac death.
PAD: Peripheral arterial disease.
CHD: Coronary heart disease.
CHF: Congestive heart failure.
MI: Myocardial infarction.
CKD: Chronic kidney disease.
CCB: Calcium channel blockers.
ACE: Angiotensin converting enzyme.
ARB: Angiotensin receptors blockers.
TRH: Treatment resistant hypertension.

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