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Review Article

A systematic review on Hypertension and conditions related to thereof

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ABSTRACT

The most frequent modifiable risk factor for death and disability is hypertension. Other modifiable risk factors include stroke, accelerated coronary and systemic atherosclerosis, heart failure, chronic kidney disease, lowering blood pressure with antihypertensive medications, and lowering the prevalence of cardiovascular disease. The 2017 American college of cardiology (ACC)/American heart association (AHA) hypertension recommendations define hypertension as systolic blood pressure (BP) greater than 130 mmHg or diastolic blood pressure (BP) less than 80 mmHg. In patients with CHD, CHF, following kidney transplantation, diabetes mellitus, and stroke, BP should be less than 130/80 mmHg. The patient was advised to modify their lifestyle by reducing their salt intake, losing weight if they were overweight, exercising regularly, drinking alcohol in moderation, and consuming more potassium-rich foods. The first antihypertensive medication should often come from one of the four types listed below: calcium channel blockers, thiazide diuretics, ACE inhibitors, and ARBs. These drugs have been found to lower cardiovascular events. Renal denervation and baroreflex activation therapy are the two interventional methods utilised in clinical practise to treat a variety of treatment-resistant hypertensions. Carotid body ablation and the implantation of an AVF are two other interventional techniques, although none of them can stop the progression of cardiovascular disease or a hypertensive patient's mortality.

INTRODUCTION

Systolic or diastolic blood pressure that is elevated above normal ranges is known as hypertension. It is prevalent in both developed and developing nations and becomes more prevalent as people age. 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]. Although in recent years hypertension has been defined as a BP of 140/90 mmHg or more. According to the 2017

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ACC/AHA guideline definition (BP 130/80 mmHg), hypertension is more prevalent generally among adults in the United States than it was under the previous definition (31.9%) [2]. Similar to this, the rate of hypertension control was 46.6% at a goal of less than 130/80 mmHg but only 61.0% among those getting therapy at a target of less than 140/90 mmHg [2].

The most important and prevalent modifiable risk factor for adult CV events and death is hypertension [3] [4]. A first MI is associated with hypertension in 69% of adults [4], a first stroke in 77% of adults [4], HF in 74% of adults [4], and PAD in 60% of older adults [5]. In addition, SCD, a dissecting aortic aneurysm, angina pectoris, LVH, thoracic and abdominal aortic aneurysms, CKD, atrial fibrillation, DM, vascular dementia, and ophthalmologic illness are all significantly increased by hypertension [6]. Treatment with antihypertensive medications that lower both BP and associated target organ damage can significantly lessen the increased risk brought on by BP rise. In all, 69 medications from 15 distinct classes—many of which are also offered as single-pill combinations—have received approval in the US for the treatment of hypertension. Despite this, there are treatment options available. RH is defined as uncontrolled blood pressure on three antihypertensive medications of different classes, one of which is a diuretic, taken at the recommended dosages or requiring four medications to control blood pressure [7] [8]. The main causes of RH are hyperaldosteronism, renal disease, Cushing syndrome, and pheochromocytoma. Refractory hypertension, which is defined as uncontrolled blood pressure on five or more medications, affects 0.5% of hypertensive patients [9]. Recent medication monitoring studies have shown that 25% to 65% of individuals with evident TRH do not adhere to BP lowering treatment [10] [11] [12] [13]. No antihypertensive medication was found in blood or urine samples in 24% to 34.5% of these patients who had been prescribed 3 to 5 antihypertensive drugs.

123 randomised trials of antihypertensive medication treatment involving 613,815 people were included in a systematic review and Meta analysis [14]. According to the review, major CV events, CHD, stroke, and heart failure (HF) substantially decreased by 20%, 17%, 27%, and 28% with every 10 mm Hg drop in SBP, respectively. This resulted in a 13% decrease in all causes of death across all populations examined [14]. Systolic blood pressure (SBP) goals of 120 or 140 mm Hg were randomly assigned to 9361 people as part of the SPRINT (systolic BP intervention experiment) [15]. These patients have a mean age of 67.9 years, a systolic blood pressure range of 130 to 180 mm Hg, elevated cardiovascular risk, no history of diabetes, stroke, or asymptomatic heart failure during the last six months, a left ventricular ejection fraction of less than 35%, and an estimated glomerular filtration rate of less than 20 ml/min/1.73 m2 [15]. At 3.26 years of follow-up, BP therapy decreased primary composite outcome or death by 22%, all causes mortality by 27%, HF by 38%, CV death by 43%, and primary composite outcome or MI by 25% [15].

BLOOD PRESSURE GOALS RECOMMENDED BY DIFFERENT GUIDELINES

According to the 2013 Eight Joint National Committee (JNC 8) guidelines for managing hypertension, those over 60 without diabetes mellitus or chronic kidney disease should have blood pressure below 150/90 mmHg, and those with diabetes mellitus and chronic kidney disease should have blood pressure below 140/90 mmHg [16]. According to the minority opinion from JNC 8, persons over the age of 80 who have hypertension but neither DM or CKD should aim for a blood pressure of less than 140/90 mmHg

[17]. The 2013 update to the UK's National Institute of Health and Care Excellence (NICE) hypertension guideline advised decreasing blood pressure in patients under the age of 80 to 140/90 mmHg [18]. These recommendations advised those under the age of 80 to decrease their blood pressure to 150/90 mmHg [18]. According to the 2014 International Society of Hypertension (ISH) standards, adults under the age of 80 should have blood pressure that is less than 140/90 mmHg [19]. These recommendations called for decreasing blood pressure in those under the age of 80 who had it above 150/90 mmHg, unless they had diabetes or kidney disease, in which case a target objective of 140/90 mmHg should be taken into consideration [19].

According to the 2015 ACC/AHA/ASH guidelines on treating hypertension in patients with CHD, the target blood pressure for adults with CHD and ACS should be less than 140/90 mmHg if they are under 80 years old, but more than 150/90 mmHg if they are over 80 years old [20]. The recommendations also recommended decreasing blood pressure in adults with CHD who have experienced a MI, a stroke, a TIA, carotid artery disease, or an abdominal aortic aneurysm to less than 130/80 mmHg.

The goal blood pressure for patients with uncomplicated hypertension should be 140/90 mmHg or below, according to the National Heart Foundation (NHF) of Australia's 2016 hypertension recommendations [21]. Systolic blood pressure should be kept under 120 mmHg in those who are at high risk for cardiovascular disease [21]. These people need to be constantly watched in order to spot treatment-related side effects such syncope, electrolyte imbalance, hypotension, and acute renal damage [21].

Three suggestions are made in the 2017 American College of Physicians (ACP)/American Academy of Family Physicians (AAFP) hypertension guidelines [22].

1) An adult under the age of 60 with a systolic blood pressure of less than 150 mmHg should have their systolic blood pressure brought down to or below 150 mmHg.
2) Systolic blood pressure should be decreased to less than 140 mmHg in those over 60 with a history of stroke or transient ischemic attack in order to limit the risk of future strokes.
3) To lower their risk of stroke and cardiovascular events, those aged 60 who have high cardiovascular risk based on individual evaluation should have their goal systolic blood pressure decreased to 140 mmHg.

As indicated in Table 1, according to the 2017 ACC/AHA hypertension guidelines, normal blood pressure is 120/80 mmHg. Elevated blood pressure is characterised as having a systolic pressure between 120 and 129 mmHg and a diastolic pressure below 80 mmHg [24]. Stage 1 hypertension is defined as systolic blood pressure of 130 to 139 mmHg or diastolic blood pressure of 80 to 89 mmHg, and Stage 2 hypertension as systolic blood pressure of 140 mmHg or lower.

For secondary prevention of recurrent CV events in adults with clinical CV disease—CHD, CHF, and stroke—and average systolic BP is 130 mmHg or average diastolic BP is 80 mmHg, the 2017 ACC/AHA hypertension guideline advised lifestyle measures with BP lowering medication. [1] [14] [25] [26]. These recommendations advocated lifestyle changes combined with blood pressure medications for those with an estimated 10-year atherosclerotic CVD (ASCVD) risk of 10% or less [27] and average systolic or diastolic blood pressure of less than 130 mmHg or less than 80 mmHg, respectively. [1] [15] [28] [29]. These recommendations called for lifestyle changes in addition to blood pressure-lowering medication for those with an estimated 10-year risk of ASCVD of 10% [27] and average blood pressure

readings of less than 140 mmHg or 90 mmHg [1] [29] [30].

The 2017 ACC/AHA hypertension recommendations advised decreasing blood pressure in adults with CHD to less than 130/80 mmHg [1] [15] [26] [28]. [31], CHF with a lower left ventricular ejection fraction [1] [32], CHF with a higher left ventricular ejection fraction [1] [32], and CKD [1] [33], following a kidney transplant [1], an adult with a Lacunars stroke [1] [34], PAD [1] [1] [25], and diabetes [1] For secondary prevention of stroke [1] [37] and ambulatory community living adult aged 65 years [1] [15] [28], as well as [35] [36].

EVALUATION OF PATIENT

Confirming the hypertension diagnosis is the first step. The suggested practise called for taking at least two blood pressure readings on at least two separate occasions using validated equipment, a correct-size cuff, and a standard measuring procedure [1]. For the diagnosis of white coat hypertension or masked hypertension, the 2017 ACC/AHA hypertension guideline advised the use of ambulatory BP measurement or home BP monitoring [1]. When blood pressure is elevated at a hospital or clinic but normal using an ambulatory monitoring technique or at home, white coat hypertension is diagnosed. One finds masked hypertension.

Table 1. Classification of BP in adult according to ACC/AHA 2017 hypertension guidelines [23].

Blood pressure Category	Definition
Normal BP	Systolic BP < 120 mmHg and diastolic BP < 80 mm Hg.
Elevated BP	Systolic BP 120 - 129 mmHg and diastolic BP < 80 mm Hg
Hypertension:	
Stage-1	Systolic BP 130 - 139 mmHg and diastolic BP 80 - 89 mm Hg.
Stage-2	Systolic BP ≥ 140 mmHg and diastolic BP ≥ 90 mm Hg

BP: Blood pressure

if blood pressure is normal at a hospital or clinic but higher when measured at home or using an ambulatory BP monitoring approach. Ambulatory blood pressure monitoring can identify symptomatic hypotension and assess mean blood pressure during the monitoring period, mean blood pressure throughout the day, and mean blood pressure during the night [1]. Following confirmation of the diagnosis, a thorough history should be conducted to evaluate any coexisting conditions and contributory variables, such as lifestyle choices, cardiovascular risk factors linked to hypertension, and features that may indicate secondary causes of hypertension. Carotid, abdominal, or femoral bruits during examination raise the risk of renal artery stenosis. Reduced femoral pulses or a difference in blood pressure between the arm and thigh may indicate aortic coarctation or severe aortoiliac illness. Abdominal striae, moon faces, or pronounced interscapular fat accumulation are indicators of Cushing illness. Primary hypertension is indicated by a steady rise in blood pressure together with weight gain and a favourable family history; secondary hypertension is indicated by many or rapid heartbeats along with target organ damage, and the most prevalent causes of secondary hypertension are mentioned in Table 2. Initial laboratory testing, as indicated in Table 3, should check for concomitant conditions that can alter a patient's reaction to medicine and check for damage to the target organ.

Table 2. Common causes of secondary hypertension [38].

Following are the common causes of secondary hypertension
• Renovascular disease.
• Coarcation of the Aorta.
• Pheochromocytoma.

• Chronic kidney disease.
• Cushing syndrome.
• Primary hyperaldosteronism
• Thyroid disease.
• Obstructive sleep apnea
• Congenital adrenal hyperplasia.

Table 3. Basic investigation of hypertension [40] [41] [42] [43] [44].

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.

An efficient screening test for primary aldosteronism is the aldosterone/renin ratio [39]. Urine samples should be taken every 24 hours while the patient consumes their typical diet. This will allow you to calculate your creatinine clearance, estimate your diet's salt and potassium consumption, and monitor your body's aldosterone excretion. For individuals in whom pheochromocytoma is suspected, measurement of 24 hour urine metanephrines or plasma metanephrines is an efficient screening tool [40]. Only those with a higher degree of suspicion for renal artery stenosis should undergo imaging. Target organ damage is indicated by a rise in left ventricular mass index and 24-hour urine albumin excretion in resistant hypertension [41].

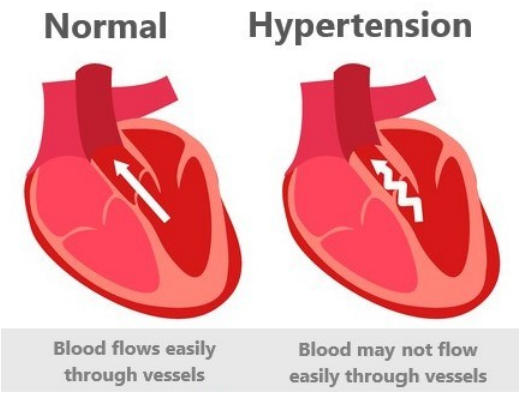

Figure 1: Blood fluidity in Hypertension condition

TREATMENT OF HYPERTENSION

There are both nonpharmacological and pharmaceutical methods for treating hypertension. The choice of treatment relies on the presence of CV, DM, and CKD. According to the 2017 AHA/ACC recommendation, patients with stage 1 hypertension who are free of these comorbidities should calculate their 10-year risk of cardiovascular disease. It is appropriate to adopt lifestyle change alone for three to six months if the risk is less than 10%. Both life style adjustment and medicine are advised for stage 2 hypertension in patients with pre-existing conditions such DM, CKD, and a 10-year CV event risk of 10% or higher.

1. Nonpharmacological Treatment

The nonpharmacologic methods for treating hypertension are listed below.

1.1. Dietary Salt Restriction: Dietary salt consumption is restricted to less than 1500 mg per day [45] [46]. In typical hypertension patients, dietary salt restriction has been shown to reduce systolic blood pressure by 5 to 10 mmHg and diastolic blood pressure by 2 to 6 mmHg.

1.2. Weight Loss: If a patient is overweight or obese, weight loss offers a demonstrable advantage in terms of lowering blood pressure and reducing the number of medications given [47]. Studies on long-term weight loss have shown that a 10 kg weight loss is connected with an average

drop of 6 mmHg in systolic blood pressure and 4.6 mmHg in diastolic blood pressure.

1.3. Physical Activity: Regular aerobic exercise resulted in an average decrease of 4 mmHg in systolic and 3 mmHg in diastolic blood pressure. Therefore, the patient is advised to engage in 90 to 150 minutes of aerobic or resistance exercise each week [48] [49]. Therefore, all hypertension patients are recommended to exercise.

1.4. Moderate Alcohol Intake: All hypertension patients are recommended to have no more than two drinks per day for males and one drink per day for women. This will lower systolic blood pressure by 3 to 8 mmHg and diastolic blood pressure by 1 to 4 mmHg [50] [51].

1.5. High Fiber and Low fat Diet: The DASH diet, which is high in low fat and low in saturated fat and is a dietary approach to end hypertension, decreased systolic blood pressure in hypertension patients by 11.4 mmHg and decreased diastolic blood pressure by 5.5 mmHg [52]. Increased intake of fruits and vegetables not only lowers blood pressure but also enhances endothelial function.

1.6. Withdrawal of Interfering Medications: If it's difficult to completely eliminate a medication that may interfere with blood pressure regulation, such as NSAIDS, the lowest effective dose should be utilised. It is important to constantly monitor blood pressure while starting therapy for hypertension with these medications since a change to the antihypertensive regimen may be required. The following medications should be avoided for treating hypertension [42].

2. Pharmacological Treatment

Target blood pressure should be less than 130/80 mmHg, according to the 2017 ACC/AHA guideline, which advised starting anti-hypertensive medication therapy with two first-line drugs from distinct classes, either separately or in a fixed dosage combination [1].

- **Initial drug selection:** Angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide type diuretics are the four groups of hypertension medications from which the first agent may be chosen [53]. Except for the major effects of beta blockers administered after MI reduced CAD event and calcium channel blockers reduced stroke, a meta-analysis of 147 randomised controlled trials involving 464,000 patients with hypertension showed that all major antihypertensive drug classes (diuretic, Angiotensin converting enzyme inhibitors, Angiotensin receptors blockers, beta blockers, and calcium channel blockers) cause reduction in CAD event and stroke for reduction in BP [54]. According to the 2011 ACC/AHA hypertension guideline, the effectiveness, tolerability, presence of certain comorbidities, and cost of antihypertensive medications should all be taken into consideration while treating adult hypertension [6].

Table 4. Medicines avoided during treatment of hypertension [42].

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

According to the 2011 ACC/AHA hypertension recommendations, diuretics, ACE inhibitors, ARBs, beta blockers, and calcium channel blockers (CCBs) may be used to treat older patients with primary hypertension [6]. According to the 2013 JNC 8 guidelines for the management of hypertension, non-black adults with primary hypertension should be treated with

diuretics, ACE inhibitors, ARBs, and calcium channel blockers [16].

According to the 2014 American society of hypertension/International society of hypertension (ASH) guideline, non-black adults with primary hypertension who are older than 60 years old should be treated with either angiotensin receptor blockers (ARBs) or ACE inhibitors [19]. According to these recommendations, non-black adults with primary hypertension who are older than 60 years old should be treated with diuretics, CCBs, ACE inhibitors, or ARBs [19]. These recommendations included the use of thiazide diuretics or calcium channel blockers in the treatment of black adults with primary hypertension [19]. The 2017 American College of Cardiology/American Heart Association hypertension guidelines are as follows [1] in relation to the use of antihypertensive medications to treat both primary and secondary hypertension:

2.1. White and Their Non-Blacks Aged <60 Years with Primary Hypertension: ACE inhibitors or ARBs should be the primary antihypertensive medicine of choice, followed by diuretics or calcium channel blockers, and if a third drug is required, a combination of ACE inhibitors or ARBs with thiazide diuretic and calcium channel blockers is used [1] [19].

2.2. White and Other Non-Blacks Aged ≥60 Years with Primary Hypertension: Thiazide diuretics or CCBs should be the initial antihypertensive medicine of choice, followed by ACE inhibitors or ARBs, and if a third antihypertensive is required, a combination of CCB + ACE inhibitors OR ARB [1] [19].

2.3. Blacks with Primary Hypertension: Thiazide diuretics or CCBs should be used as the initial antihypertensive medication, and if a third antihypertensive is required, a combination of thiazide diuretics, CCBs, ACE inhibitors, or ARB should be used [1] [19].

2.4. Stable Coronary Heart Disease with Hypertension: If a third antihypertensive medicine is required, beta blockers plus ACE inhibitors or ARB plus thiazide diuretics or CCBs should be given [1] [20] [54] [55]. Patients with stable CAD and hypertension are treated with beta blockers plus ACEs inhibitors or ARBs.

2.5. Heart Failure with Reduced Left Ventricular Ejection Fraction and Hypertension:

Patients with heart failure (HF) who have high blood pressure and a reduced left ventricular ejection fraction are treated with beta blockers (carvedilol, metoprolol, and bisoprolol), ACE inhibitors, or ARBs, combined with diuretics. [1] [32] [56] [57] [58] [59] [60].

2.6. Heart Failure with Preserved Left Ventricular Ejection Fraction: Patient with maintained left ventricular ejection fraction, hypertension, and HF should have volume overload, therefore hypertension is treated with beta blockers, ACE inhibitors, or ARSs, as well as antagonists of the mineralocorticoid receptors. [1] [32] [61] [62].

2.7. Chronic Kidney Disease with Heart Failure: Patients with high blood pressure and CKD stage 3 or above, stage 1 or stage 2, and albuminuria less than 300 mg per day should get ACE inhibitor treatment to halt the course of the disease [1] [33] [63] [64] [65]. Patients should be treated with ARBs if they cannot tolerate ACEs inhibitors [1]. First-line antihypertensive medication should be used to treat adults with stage 1 or 2 CKD who do not have albuminuria [1]. Give either ACE inhibitors or ARB together with thiazide diuretic and CCBs if three antihypertensive medications are required. To increase glomerular filtration rate and increase kidney survival following kidney donation, hypertension is treated with CCBs [1] [66].

2.8. Stroke or Transient Ischemic Attack with Hypertension: Thiazide diuretics, ACEs

inhibitors, or ARBs should be used to treat hypertensive patients who have experienced a stroke or transient ischemic attack [1] [67] [68] [69]. If a third antihypertensive medication is required, a thiazide diuretic together with an ACE inhibitor or an ARB along with CCB should be administered.

2.9. Peripheral Arterial Disease and Hypertension: Patients with PAD and hypertension should receive the same first-line antihypertensive medications as patients without peripheral vascular disease, including diuretics, ACE inhibitors, ARBs, CCBs, and beta blockers [1] [70].

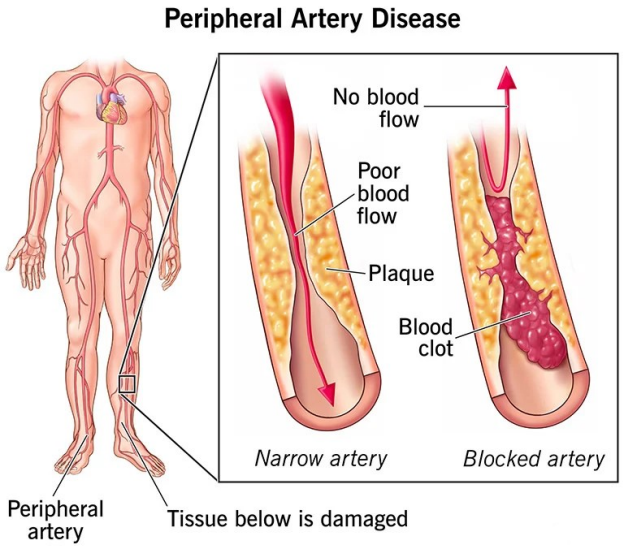

Figure 2: Peripheral Arterial Disease (PAD)

2.10. Hypertension and Diabetes Mellitus: Thiazide diuretics, ACE inhibitors, or ARBs should be used to treat patients with hypertension and diabetes mellitus [1] [35] [71]. Initial therapy with ACE inhibitors or ARBs is recommended for individuals with diabetes mellitus, hypertension, and chronic albuminuria [1] [72] [73].

2.11. Thoracic Aortic Aneurysm and Hypertension: For patients with hypertension with a thoracic aortic aneurysm, beta blockers are the antihypertensive medications of choice [25]. In cases of aortic dissection, beta blockers are also linked to increased and improved survival [1] [74].

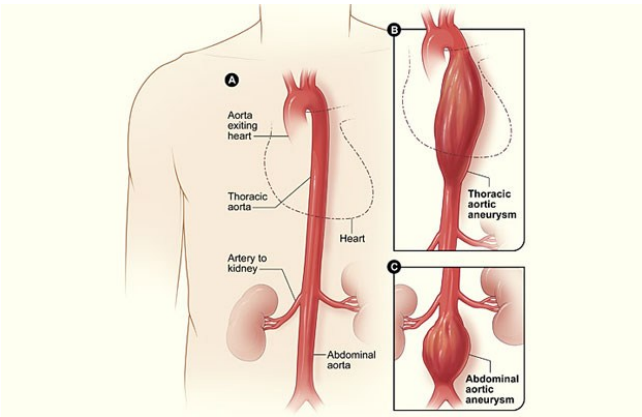

Figure 3: Thoracic Aortic Aneurysm

2.12. Hypertension and Pregnancy: Direct renin inhibitors, ACE inhibitors, ARBs, and atenolol should not be used to treat pregnant women with hypertension [1] [75] [76] [77]. In patients with hypertension during pregnancy, methyldopa, hydralazine, nifedipine, and labetalol are preferred medications [1] [78].

2.13. Resistant Hypertension: RH was treated with lifestyle changes, the diagnosis and treatment of secondary hypertension, and the management of obesity and other comorbidities [1] [24]. Spironolactone should be added to the treatment regimen if a fourth antihypertensive medication is necessary to manage blood pressure [79].

NEW APPROACH FOR TREATMENT OF HYPERTENSION

1. Part 1: New Drugs for Treatment of Hypertension

1.1. Antialdosterone Agent: Aldosterone is a mineralocorticoid that controls the body's electrolyte and water balance. When the amount of aldosterone is raised, it can lead to the development of hypertension as well as other diseases such myocardial fibrosis, myocardial hypertrophy, and heart failure [80]. A volume-expanded type of hypertension results from the action of aldosterone on the mineralocorticoid receptor in the cortical collecting duct of the nephron and mineralocorticoid receptors stimulating expression of sodium channels. The mitochondrial cytochrome P450 enzyme

aldosterone synthase, which is encoded by the CYP11B2 gene, converts 11-deoxycorticosterone into aldosterone in the zonaglomerulosa of the adrenal cortex [81].

- **Mineralocorticoid Receptor Antagonists -** Spironolactone, a mineralocorticoid receptor antagonist, is being utilised as an add-on medication in patients with RH and has a small ability to reduce blood pressure. Due to spirolactone's structural resemblance to progesterone and lack of selectivity for the mineralocorticoid receptor at higher doses, it has been used sparingly since it can have negative effects on both men and women. Plerenone is a more selective mineralocorticoid receptor antagonist than spironolactone, but it is less powerful and has a shorter half-life (3–4 h), which reduces its antihypertensive effectiveness and necessitates twice-daily dosing. The development of BAY 94 - 886 (finerenone), a nonsteroidal MRA with greater selectivity for the MR over other steroid hormone receptors than spironolactone, greater affinity for the MR than Eplerenone, and no effect on the L-type calcium channel, was made possible by the optimisation of the MRA activity of the dihydropyridine compound [82] [83]. Finerenone has improved myocardial function and increased cardiac activity without compromising renal sodium potassium balance. Finerenone provides higher cardio-renal target organ protection than steroidal mineralocorticoid receptor antagonist in preclinical models of hypertension-related heart failure and renal disease [84].
- **Aldosterone Synthase Inhibitors -** In animal models of hypertension and heart failure, LCI699, the first orally active aldosterone synthase inhibitor, reduces plasma and urine aldosterone concentration, raises plasma renin activity, and prevents target organ damage. Similar effects on aldosterone and renin levels have been seen in hypertensive patients [88] [89] as well as in healthy persons [85] [86]. The effectiveness and safety of various dosages of LCI699 with eplerenone were compared in the first randomised double-blind, placebo-controlled study of LCI699, which involved 524 individuals with primary hypertension [89]. Significant decreases in office systolic blood pressure were reported with all dosages of LCI699 and were on par with those seen with eplerenone. Both LCI699 and eplerenone were well tolerated drugs that decreased plasma aldosterone levels while raising them.

1.2. Vasopeptidase Inhibitors: Because it breaks down the natriuretic peptides atrial natriuretic peptide (ANP), B type natriuretic peptide (BNP), and urodilatin, the zinc metalloprotease neprilysin is a therapeutic target for hypertension and other types of cardiovascular disease [90]. An increase in circulating natriuretic peptide levels that results from neprilysin inhibition causes natri

- **Natriuretic Peptide Receptor Agonist** In order to treat heart failure and refractory or RH, natriuretic peptide receptor agonists are being developed as an alternative to blocking the breakdown of endogenous natriuretic peptides. The synthetic molecule PL-3994, an agonist of the natriuretic peptide receptor A (NPR-A), contains an amino acid mimic and has decreased affinity for the natriuretic peptide clearance receptor (NPR-C) and increased resistance to neprilysin, resulting in a prolonged half-life after subcutaneous administration [91]. In comparison to a placebo, healthy volunteers receiving a single subcutaneous dosage of PL-3994 had greater natriuresis and diuresis as well as a decrease in systemic blood pressure. A phase II trial in hypertension-prone volunteers who were taking one antihypertensive drug showed a

decrease in systemic BP compared to placebo. Particularly, PL-3994 showed to interact well with ACE inhibitors, indicating that it may be given as an additional treatment to patients with refractory RH or HF.

1.3. Dopamine β-Hydroxylase Inhibitor: A therapeutic target for the treatment of hypertension and other cardiovascular illnesses characterised by sympathetic activation in HF is dopamine -hydroxylase, the enzyme that catalyses the hydroxylation of dopamine to generate noradrenaline in the sympathetic nervous system. Theoretically, Dopamine -hydroxylase inhibition is superior than adrenergic receptor blockade: 1) It slows down sympathetic activity gradually; 2) It makes more dopamine available, leading to renal vasodilatation, natriuresis, and diuresis. Disulfiram, fusaric acid, and nepicastat, among other first, second, and early third generations D'H inhibitors, were not therapeutically beneficial due to their lack of efficacy or selectivity for D'H or because they had significant CNS-related side effects. When taken orally, etamicastat is a strong and reversible inhibitor of dopamine hydroxylase that does not cross blood-brain barriers, making it selective for peripheral dopamine hydroxylase. Good tolerance and substantial dose-dependent reductions in 24-h ambulatory BP were seen in studies of healthy men and individuals with mild to severe hypertension [92].

5.2. Part 2: Interventional Approach for Treatment of Hypertension

Interventional techniques are indicated as a therapy option for a number of treatment-resistant hypertensions for the management of arterial hypertension.

2.1. Renal Denervation: Numerous publications dealing with RDN have been published in this field of study, which is expanding quickly. The development, maintenance, and acceleration of arterial hypertension are all significantly influenced by increased sympathetic activity [93] [94]. When the kidney's efferent sympathetic nerve is activated, renin is released, tubular salt and water absorption is improved, and renal blood flow is decreased. As a result, blood volume increases and blood pressure is elevated. In essential hypertension, the renal sympathetic outflow is active, and the main goal of treatment is to use an endovascular approach to stop this activation and lower blood pressure. Renal denervation using a catheter has been proposed as a novel interventional strategy that targets sympathetic nerve activity. Radiofrequency catheter ablation of renal sympathetic nerves has received a lot of positive attention. With today's multielectrode denervation technology, four ablations may be done for each renal artery in a single, quick treatment, resulting in more thorough ablations. Randomised research (Symplicity HTN-2 trial) with 106 patients showed a mean decrease in office systolic and diastolic blood pressure of 32/12 mmHg at 6 months, respectively [95] and this effect was sustained after 2 years of follow-up. However, since only a limited subset of ambulatory blood pressure monitoring data was available, the results, which were based on office BP, showed a less striking BP decline. After six months, (11/7 mmHg in 24-h BP) [95]. Furthermore, it is unclear if the BP decrease persisted during a lengthy follow-up [96]. The use of the renal sympathetic denervation is restricted to patients with more severe RH whose ambulatory blood pressure is still uncontrolled after the use of four or more antihypertensive medications, including blockers of mineralocorticoid receptors. In addition to lowering blood pressure, renal denervation also improves glucose metabolism, has a protective impact against end organ damage such LVH, arterial stiffness, and albuminuria, and improves the functional status of patients with congestive heart failure.

2.2. Baroreflex Activation Therapy: Baroreflex activation treatment is a surgically implanted device that reduces sympathetic response and, as a result, lowers blood pressure by electrically activating carotid sinus baroreceptors. A randomized, double-blind, placebo-controlled device study was done in individuals with hypertension as part of the Rheos pivotal trial [97]. After a year, there was a mean decrease in office systolic blood pressure of up to 35 mmHg, and more than 50% of the participants had systolic blood pressure under control. Over a lengthier 22–53 month follow-up, this impact persisted. It is significant to note that this research only assessed office BP decrease; ambulatory BPs were not evaluated. Ambulatory blood pressure was assessed in a comparable experiment (DEBuT—Device Based Therapy) carried out in Europe [98]. After a year, office systolic blood pressure decreased by 30 mmHg, but ambulatory systolic blood pressure decreased on average by 13 mmHg. As a result, this procedure's future is uncertain, and several issues have not yet been fully resolved. Additional research is needed to assess the long-term safety and determine whether the addition of new medications will cause an ambulatory blood pressure drop.

2.3. Carotid Body Ablation: Ablation of the carotid body Studies on human and animal subjects [95] showed that hypertension increased carotid body sensitivity, however the cause of abnormality is unknown. Deactivating CB chemoreceptors with hyperoxia (respiration with 100% oxygen) in a small, randomized, crossover, placebo-controlled research reduced the increased muscular sympathetic nerve activity in untreated hypertensive males, but no effect was seen in controls [96]. Additionally, it has been demonstrated that hyperoxia lowers blood pressure abruptly in hypertensive patients but not in normotensive controls. These findings suggest that tonic chemoreceptor drive may have a pathogenetic role in the emergence of sympathetic overactivity in hypertension [99]. Humans have had surgical carotid body excision for conditions other than hypertension. (bronchial asthma, COPD). After 5 days after carotid body removal and continuing for 6 months after bilateral carotid body surgery, a hypertensive patient's blood pressure dropped from 170 to 130 mmHg, although a normotensive patient's blood pressure remained unaffected. As of this writing, no research examining the impact of unilateral or bilateral carotid body excision for hypertension in humans has been finished, however studies on this topic are being conducted in men.

2.4. Arteriovenous Fistula: The self-expanding device quickly produces a sustained calibrated shunt volume of 800 ml/minute by forming a 4 mm AVF between the iliac artery and vein. (1 Hour). After the development of AVF, many processes are thought to reduce BP [100]. The primary mechanism is a decrease in total systemic vascular resistance despite an increase in cardiac output. Increased arterial oxygen content may improve tissue oxygen delivery by reducing peripheral and renal chemoreceptor activation, which in turn reduces sympathetic activity. As a result of improved arterial compliance and decreased systemic vascular compliance, even with higher cardiac output, the workload on the heart may be reduced [100]. In the first randomised controlled study of this method at 6 months, the intervention group had a decrease in office systolic blood pressure of 27 mmHg as opposed to a decline of 4 mmHg in the standard care group, which was supported by ambulatory blood pressure monitoring. Because of the potential for venous stenosis, thrombosis, and the development of right HF, this medication is rarely prescribed.

2.5. Renal artery Stenting: For renal artery stenosis, percutaneous transluminal angioplasty with stenting is debatable. Recent clinical investigations showed that using the renal artery

has little to no advantage for controlling blood pressure, maintaining kidney function, or preventing cardiovascular or renal events. Stenting in a patient with high blood pressure and renal artery stenosis [101] [102]. The preferred method of treating hypertension is angioplasty of fibromuscular lesions since it virtually always has positive effects and is frequently curative of the accompanying hypertension. When medication treatment fails, endovascular angioplasty with or without stenting should be taken into consideration for poorly controlled hypertension with CV risk. Renal artery revascularization did not lower blood pressure in a clinically meaningful way in the ASTRAL study, but it did result in a high rate of complications from the treatment, making it less prevalent.

CONCLUSION

For secondary prevention of recurrent cardiovascular events in people with clinical CVD (CHD, CHF, and stroke) with an average systolic BP > 130 mmHg or an average diastolic BP > 80 mmHg, combine lifestyle changes with blood pressure-lowering medications. A SBP > 160 mmHg despite therapy with an average of 5 different antihypertensive medications qualifies as an interventional BP lowering treatment when it is administered to individuals with TRH. The two interventional techniques that are most frequently employed in clinical practise are baroreflex activation treatment and renal denervation, whereas AVF and renal artery stenting are not. In patients with diabetes mellitus, CHF, CKD, following kidney transplantation, and for secondary stroke prevention in lacunar stroke, the blood pressure should be less than 130/80 mmHg. As the initial medication prescribed, a thiazide diuretic, an ACE inhibitor, or an ARB is begun, followed by a follow-up blood pressure and electrolyte assessment in three to four weeks. There may be a need for a dose increase or extra medicine. Regular visits are advised during dosage modification; in addition to home blood pressure monitoring, each visit should include an evaluation of lifestyle variables and medication adherence. We advise follow-up at 6-month intervals after the blood pressure is below 130/80 mmHg.

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