

# Treatment of Hypertension: A Review

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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  $\geq 130$  mmHg or diastolic BP is  $\geq 80$  mmHg. BP should be lower than 130/80 mmHg in patient with CHD, CHF, after renal transplantation, diabetes mellitus and stroke. Recommended lifestyle modification included restriction of dietary sodium intake, weight loss if patient is overweight, regular exercise, moderate alcohol intake and increase consumption of potassium rich foods. 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 hypertension. 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

## 1. Introduction

Hypertension is the elevation of systolic BP, diastolic BP, or both above normal levels, is common in developed and developing countries and increases in pre-

valence 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,  $\geq 140/90$  mmHg) and is 45.6% according to the 2017 ACC/AHA guideline definition (BP  $\geq 130/80$  mmHg) [2]. 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 [2].

Worldwide, hypertension is the leading modifiable and major risk factor for CV events and mortality in adult [3] [4]. Hypertension is present in 69% of adults with a first MI [4], in 77% of adults with a first stroke [4], in 74% of adults with HF [4], and in 60% of older adults with PAD [5]. 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 ophthalmologic disease [6]. 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  $\geq 3$  antihypertensive drugs of different classes, in which one of them is diuretic, at optimal doses or requiring  $\geq 4$  drug to control blood pressure [7] [8] and causes of RH are primarily hyperaldosteronism, Renovascular disease, Cushing syndrome and Pheochromocytoma. In addition,  $\approx 0.5\%$  of hypertensive patients have refractory hypertension, defined as uncontrolled BP on  $\geq 5$  drugs [9]. Recent drug monitoring studies have revealed no adherence to BP lowering therapy in 25% to 65% of patients with apparent TRH [10] [11] [12] [13]. In 24% to 34.5% of these individuals, who were prescribed 3 - 5 antihypertensive medications, no antihypertensive medication was detected in blood or urine samples.

A systematic review and Meta analysis included 123 randomized studies of antihypertensive drug therapy in 613,815 individuals [14]. The review found that every 10 mm of Hg decrease in SBP significantly decreased major CV event by 20%, CHD by 17%, stroke by 27%, and HF by 28%, which in all populations studied reduced all causes of mortality by 13% [14]. SPRINT (systolic BP intervention trial) randomized 9361 adults to a systolic BP goal of  $< 120$  mm of Hg or  $< 140$  mm of Hg [15]. These patients have mean age of 67.9 years, systolic BP 130 - 180 mm of Hg and increased CV risk, no DM, history of stroke, or asymptomatic HF within the past 6 months, left ventricular ejection fraction  $< 35\%$ , and estimated glomerular filtration rate  $< 20$  ml/min/1.73 m<sup>2</sup> [15]. At 3.26 years follow up BP treatment reduced the primary composite outcome of MI, stroke, HF,

or death from CV causes by 25%, all causes mortality by 27%, HF by 38%, CV death by 43% and primary composite outcome or death by 22% [15].

## 2. Blood Pressure Goals Recommended by Different Guidelines

The 2013 Eight Joint National Committee (JNC 8) guidelines for management of hypertension recommended lowering BP to <150/90 mmHg in adult aged  $\geq 60$  years without diabetes mellitus or Chronic kidney disease and <140/90 mmHg in adult with diabetes mellitus chronic kidney disease [16]. The minority view from JNC 8 recommended that the BP goal in adults aged <80 years with hypertension without DM or CKD should be <140/90 mmHg [17]. The UK National Institute of health and Care Excellence (NICE) hypertension guideline, update in 2013 recommended lowering BP to <140/90 mmHg in aged <80 years [18]. These guidelines recommended lowering BP to <150/90 mmHg in adult aged  $\geq 80$  years [18]. The 2014 international society of hypertension (ISH) guidelines recommended reducing BP to <140/90 mmHg in adult aged  $\leq 80$  years [19]. These guidelines also recommended lowering BP to <150/90 mmHg in adult aged  $\geq 80$  years with BP  $\geq 150/90$  mmHg unless these adult have DM or CKD in which case a target goal of <140/90 mmHg should be considered [19].

The ACC (American college of cardiology)/AHA (American heart Association)/ASH (American society of hypertension) 2015 guidelines on treatment of hypertension in patient with CHD recommended that target BP should be < 140/90 mmHg in adult with CHD and ACS if aged  $\leq 80$  years but <150/90 mmHg if they are aged  $\geq 80$  years [20]. These guidelines also stated that lowering BP to <130/80 mmHg in adult with CHD who have had a MI, stroke, TIA, carotid artery disease, abdominal aortic aneurysm.

The National Heart Foundation (NHF) of Australia 2016 hypertension guidelines state that in patient with uncomplicated hypertension target BP should be <140/90 mmHg or lower [21]. In selected high CV risk individual target systolic BP should be <120 mmHg can improve CV outcome [21]. These adults should have closely monitored to identify treatment related adverse effect, including hypotension, syncope, electrolyte imbalance and acute kidney injury [21].

The 2017 American college of physicians (ACP)/American Academy of Family physician (AAFP) hypertension guidelines give three recommendations [22].

1) Adult aged  $\geq 60$  years with systolic blood pressure  $\geq 150$  mmHg should have systolic BP reduced to <150 mmHg to reduce the risk of mortality, stroke, and cardiovascular event.

2) Adult aged  $\geq 60$  years with history of stroke or Transient ischemic attack should have reduced systolic BP to <140 mmHg to decrease the risk of recurrent stroke.

3) Adult aged  $\geq 60$  years at high cardiovascular risk based on individual assessment should have target systolic BP reduced to <140 mmHg to reduce their risk for stroke and cardiovascular event.

The 2017 ACC/AHA hypertension guidelines stated that normal BP is

<120/80 mmHg [23] as shown in **Table 1**. Elevated BP was defined as systolic BP is 120 - 129 mmHg with diastolic BP is <80 mmHg and should be treated with life style measure [24]. Stage 1 hypertension is systolic BP is 130 - 139 mmHg or diastolic BP is 80 - 89 mmHg and Stage 2 hypertension is systolic BP  $\geq$  140 mmHg or diastolic BP is  $\geq$ 90 mmHg.

The 2017 ACC/AHA hypertension guideline recommended lifestyle measure plus BP lowering drug for secondary prevention of recurrent CV event in adult with clinical CV disease—CHD, CHF and stroke and average systolic BP is  $\geq$ 130 mmHg or average diastolic BP is  $\geq$ 80 mmHg [1] [14] [25] [26]. These guidelines recommended lifestyle measure plus BP lowering drug for primary prevention of CV disease in adult with an estimated 10 years risk of atherosclerotic CVD (ASCVD)  $\geq$  10% [27] and average systolic BP is  $\geq$ 130 mmHg or an average diastolic BP is  $\geq$ 80 mmHg [1] [15] [28] [29]. These guidelines recommended lifestyle measure plus BP lowering drug for primary prevention of CV in adult with estimated 10 years risk of ASCVD < 10% [27] with an average systolic BP is  $\geq$ 140 mmHg or an average diastolic BP is  $\geq$ 90 mmHg [1] [29] [30].

The 2017 ACC/AHA hypertension guidelines recommended lowering BP to <130/80 mmHg in adult with CHD [1] [15] [26] [28] [31], CHF with reduced left ventricular ejection fraction [1] [32], CHF with preserved left ventricular ejection fraction [1] [32], CKD [1] [33], after renal transplantation [1], adult with Lacunars stroke [1] [34], PAD [1] [25], DM [1] [35] [36], for secondary prevention of stroke [1] [37] and ambulatory community dwelling adult aged 65 year [1] [15] [28].

### 3. Evaluation of Patient

The first step is to confirm the diagnosis of hypertension. The guideline recommended at least two BP measurement on at least two occasions with use of standard measurement technique, validated equipment, including cuff of correct size [1]. The 2017 ACC/AHA hypertension guideline recommended the use of ambulatory BP measurement or home BP monitoring for the diagnosis of white coat hypertension or masked hypertension [1]. White coat hypertension is diagnosed when BP is increased in hospital or clinic but normal in ambulatory BP monitoring technique or home BP monitoring. Masked hypertension is diagnosed

**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.
<b>Hypertension:</b>	
Stage-1	Systolic BP 130 - 139 mmHg and diastolic BP 80 - 89 mm Hg.
Stage-2	Systolic BP $\geq$ 140 mmHg and diastolic BP $\geq$ 90 mm Hg.

BP: Blood pressure.

if BP is normal in hospital or clinic but increased in ambulatory BP monitoring technique or in home BP monitoring. Ambulatory blood BP monitoring can measure the BP while patient perform normal daily activities and can measure mean BP during the entire monitoring periods, means BP during day and night time and diagnosed the symptomatic hypotension [1]. Once the diagnosis is confirmed, a complete history should be taken to assess the coexisting condition and contributing factors including lifestyle, CV risk factors associated with hypertension and feature suggest secondary causes of hypertension. On examination if presence of carotid, abdominal or femoral bruits increase the possibility of renal artery stenosis. Diminished femoral pulses or a discrepancy between arm and thigh blood pressure suggests aortic coarctation or significant aortoiliac disease. Cushing disease is suggested by abdominal striae, moon faces or prominent interscapular fat deposition. A gradual rise in BP that associated with weight gain with positive family history suggests primary hypertension where as several or RH with target organ damage suggests secondary hypertension and common causes of secondary hypertension listed in **Table 2**. Initial laboratory investigation shown in **Table 3**, should assess for coexisting condition that may affect patient response to medication and assess for target organ damage.

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

Following are the common causes of secondary hypertension
<ul style="list-style-type: none"> <li>▪ Renovascular disease.</li> <li>▪ Coarctation of the Aorta.</li> <li>▪ Pheochromocytoma.</li> <li>▪ Chronic kidney disease.</li> <li>▪ Cushing syndrome.</li> <li>▪ Primary hyperaldosteronism.</li> <li>▪ Thyroid disease.</li> <li>▪ Obstructive sleep apnea.</li> <li>▪ Congenital adrenal hyperplasia.</li> </ul>

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

Following are the basic investigation of hypertension:
<ul style="list-style-type: none"> <li>• Complete blood count-TLC, DLC, Hb %, RBC</li> <li>• Renal function test-Blood urea, serum creatinine, potassium, Sodium, calcium, uric acid</li> <li>• Blood sugar level</li> <li>• Urinalysis</li> <li>• Lipid profile</li> <li>• Thyroid function test</li> <li>• Electrocardiography</li> <li>• Urine albumin to creatinine ratio</li> <li>• Measure plasma aldosterone/Renin ratio</li> <li>• Measurement of 24 hours urinary metanephrines.</li> </ul>

The aldosterone/renin ratio is effective screening test for primary aldosteronism [39]. 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 [40]. 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 [41].

## **4. 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 implement 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.

### **4.1. Nonpharmacological Treatment**

Following are the nonpharmacologic way to treatment of hypertensions.

#### **4.1.1. Dietary Salt Restriction**

The restriction dietary sodium intake is below 1500 mg per day [45] [46]. The benefit of dietary salt reduction is well documented in general hypertensive patient in whom associated with reduction of 5 to 10 mmHg in Systolic BP and 2 to 6 mmHg diastolic BP.

#### **4.1.2. Weight Loss**

Weight loss has a clear benefit in term of reducing of blood pressure and also reduce the number of prescribed medicine so weight loss if the patient is overweight or obese [47]. Long term weight loss studies have indicated that 10 kg weight loss is associated with average reduction of systolic BP 6 mmHg and diastolic BP is 4.6 mmHg.

#### **4.1.3. Physical Activity**

The regular aerobic exercise produced average reduction of systolic BP 4 mmHg and 3 mmHg in diastolic BP. So patient is advice for aerobic or resistance exercise for 90 to 150 minute per week [48] [49]. So all patient of hypertension encouraged to do exercise.

#### **4.1.4. Moderate Alcohol Intake**

All patient of hypertension advised for moderate of alcohol intake— $\leq 2$  drinks daily for men and  $\leq 1$  drink per day for woman will reduce systolic BP by 3 to 8

mmHg and diastolic BP by 1 to 4 mmHg [50] [51].

#### 4.1.5. High Fiber and Low fat Diet

Ingestion of diet rich in fruits and vegetable, potassium, magnesium, calcium, high in low fat diet and low in saturated fat that is dietary approach to stop hypertension (DASH) reduced systolic BP in hypertension patient by 11.4 mmHg and reduced diastolic BP by 5.5 mmHg [52]. High amount of fruit and vegetables in diet not lower the BP but also improve endothelial function.

#### 4.1.6. Withdrawal of Interfering Medications

Medicine that may interfere with BP control, mainly NSAIDS should be voided or if complete avoidance is difficult the lowest effective dose should be used. When initiating treatment of hypertension with these agents should monitored BP closely because adjustment to antihypertensive regimen may become necessary. Following medicine shown in **Table 4** should be avoided during treatment of hypertension [42].

## 4.2. Pharmacological Treatment

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 [53]. 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 reduction in BP [54]. 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 comorbidities and cost [6].

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

Following are the medicines during treatment of hypertension:
<ul style="list-style-type: none"> <li>• Non steroidal anti-inflammatory drugs</li> <li>• Oral contraceptives pills</li> <li>• Corticosteroids</li> <li>• Tricycle antidepressant drugs</li> <li>• Monoamine oxidase inhibitors</li> </ul>

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) [6].

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 [16].

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) [19]. These guidelines recommended that non black adult with age  $\geq 60$  years with primary hypertension is treated with diuretics, CCBs, ACE inhibitors or ARBs [19]. These guidelines also recommended that black adult with primary hypertension is treated calcium channel blockers or thiazide diuretics [19].

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]:

#### **4.2.1. 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 [1] [19].

#### **4.2.2. White and Other Non Blacks Aged $\geq 60$ 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 [1] [19].

#### **4.2.3. 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 [1] [19].

#### **4.2.4. 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 [1] [20] [54] [55].

#### **4.2.5. 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 [1] [32] [56] [57] [58] [59] [60].

#### **4.2.6. Heart Failure with Preserved Left Ventricular Ejection Fraction**

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 ARBs plus mineralocorticoid receptors antagonist [1] [32] [61] [62].

#### **4.2.7. Chronic Kidney Disease with Heart Failure**

Patient with hypertension and CKD stage-3 or higher or stage-1 or stage-2 with albuminuria  $\geq 300$  mg/day should be treated with ACEs inhibitors to slow progression of CKD [1] [33] [63] [64] [65]. 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 [1] [66].

#### **4.2.8. 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 [1] [67] [68] [69]. If third antihypertensive drug is needed then give thiazide diuretic plus ACE inhibitors or ARBs plus CCB should added.

#### **4.2.9. 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 [1] [70].

#### **4.2.10. Hypertension and Diabetes Mellitus**

In patient with hypertension and diabetes mellitus should be treated with ACEs inhibitors or ARBs, CCBs and thiazide diuretic [1] [35] [71]. If patients with diabetes mellitus, hypertension and persistent albuminuria, initial treatment with ACEs Inhibitors or ARBs [1] [72] [73].

#### **4.2.11. Thoracic Aortic Aneurysm and Hypertension**

Beta blockers are preferred antihypertensive drug for patient with hypertension and thoracic aortic aneurysm [25]. Beta blockers are also associated with increase improved survival in aortic dissection [1] [74].

#### **4.2.12. Hypertension and Pregnancy**

Women with hypertension who become pregnant should not treat with ACEs inhibitors, ARBs, direct renin inhibitors or atenolol [1] [75] [76] [77]. Methyldopa, Hydralazine, Nifedipine, and Labetalol is a drug of choice in patient with hypertension and pregnancy [1] [78].

#### **4.2.13. Resistant Hypertension**

Treatment of RH included detection and treatment of secondary hypertension, use of life style measure and treat obesity and other comorbidities [1] [24]. If fourth antihypertensive drug is required to control blood pressure then give mineral ocorticoids receptors antagonist that is spironolactone in the therapeutic regimen [79].

### **5. New Approach for Treatment of Hypertension**

#### **5.1. Part 1: New Drugs for Treatment of Hypertension**

##### **5.1.1. 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 [80]. 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-deoxycorticosterone in the zonaglomerulosa of adrenal cortex through the action of mitochondrial cytochrome P450 enzyme, aldosterone synthase which is encoded by the CYP11B2 gene [81].

##### **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 antiandrogenic activity 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), 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 [82] [83]. 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 [84].

##### **Aldosterone Synthase Inhibitors**

LCI699, 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 [85] [86], Similar effects on aldosterone and renin level seen in healthy humans [87] and in hypertensive patients [88] [89]. 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 [89]. 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.

### 5.1.2. 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 [90] 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.

#### Natriuretic Peptide Receptor Agonist

Natriuretic peptide receptor agonists are developed as alternative approach to inhibiting the degradation of endogenous natriuretic peptides for the treatment of heart failure and refractory or RH. The natriuretic peptide receptor A (NPR-A) agonist PL-3994 is a synthetic molecule that contains an amino acid mimetic and has reduced affinity for the natriuretic peptide clearance receptor (NPR-C) and increased resistance to neprilysin, resulting in a prolonged half-life after subcutaneous administration [91]. A phase I trial of a single subcutaneous dose of PL-3994 in healthy volunteers showed increased natriuresis and diuresis and reduction in systemic BP compared with placebo. A phase II trial in volunteers with hypertension who were receiving  $\geq 1$  antihypertensive medications demonstrated a reduction in systemic BP compared with placebo. In particular, PL-3994 appeared to act synergistically with ACE inhibitors, suggesting that it could be administered as an adjunct to standard therapy in patients with refractory or RH or HF.

### 5.1.3. Dopamine $\beta$ -Hydroxylase Inhibitor

Dopamine  $\beta$ -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  $\beta$ -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  $D\beta H$  inhibitors, for example, disulfiram, fusaric acid, and nepicastat, either lacked potency or selectivity for  $D\beta H$  or caused severe CNS-related adverse effects and thus were not clinically useful. Etamicastat is potent and revers-

ible inhibitors of Dopamine  $\beta$ -hydroxylase that not cross the blood brain barriers thus selective for peripheral Dopamine  $\beta$ -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 [92].

## **5.2. Part 2: Interventional Approach for Treatment of Hypertension**

For the management of arterial hypertension, interventional strategies are mentioned as a therapeutic option for several treatment resistant hypertension.

### **5.2.1. Renal Denervation**

This is rapidly growing research field with numerous published papers dealing with RDN. Increased sympathetic activity plays an important role in development, maintenance and acceleration of arterial hypertension [93] [94]. Activation of efferent sympathetic nerve in kidney stimulate renin release, enhance tubular reabsorption of sodium and water and decrease renal blood flow resulting blood volume will increase and BP raised. Renal sympathetic outflow is activated in essential hypertension, and basically the aim of the treatment is, by endovascular technique, to interrupt this activation causing BP reduction. Catheter based Renal Denervation has been introduced as a new interventional approach targeting the sympathetic nerve activity. The ablation of renal sympathetic nerves with a radiofrequency catheter has been evaluated with great enthusiasm. The multielectrode Denervation system available now allow 4 ablation to be performed with single short treatment time for each renal artery and provide more complete ablations. A randomized study (Symplicity HTN-2 trial) enrolled 106 patients and demonstrated a mean reduction of 32/12 mmHg at 6 months in office systolic and diastolic BP, respectively [95] and this effect was maintained after 2 years of follow-up. Nevertheless, the results were based on office BP where as Ambulatory BP monitoring data were available only in a small subgroup, showing a less impressive BP reduction (11/7 mmHg in 24-h BP) after 6 months [95]. Moreover, it is not clear if BP reduction was sustained over long-term follow-up [96]. The renal sympathetic Denervation shall be reserved to more severe RH patient, in whom ambulatory BP remain uncontrolled despite using four or more antihypertensive drug including mineralocorticoid receptors blockers. Other effects of renal Denervation beyond the BP reduction include improvement of glucose metabolism, beneficial effect on end organ damage, for example, LVH, arterial stiffness, and albuminuria and improvement in functional status in patient with congestive HF.

### **5.2.2. Baroreflex Activation Therapy**

Baroreflex activation therapy is surgically implantable device, work by electrical stimulating carotid sinus baroreceptors, causes reduction in sympathetic response and consequently BP reduction. The rheos pivotal trial [97] was a doub-

leblind, randomized, placebo-controlled device trial conducted in hypertension patients. There was a mean reduction in office systolic BP of up to 35 mmHg after 12 months, and over 50% of subjects achieved systolic BP control. This effect was sustained over longer follow-up of 22 - 53 months. It is important to note that this trial did not evaluate ambulatory BPs, just office BP reduction. A similar trial conducted in Europe (DEBuT—Device Based Therapy) evaluated ambulatory BP [98]. After 12 months, office systolic BP was reduced in 30 mmHg, whereas ambulatory systolic BP showed a mean reduction of 13 mmHg. Therefore, the future of this procedure is uncertain and some doubt are not completely clarified yet. More investigation is required about the long term safety and to evaluate whether the reduction in ambulatory BP with addition of some new drugs.

### 5.2.3. Carotid Body Ablation

Carotid body ablation Studies in animal model and human subject [95] revealed enhanced carotid body sensitivity in hypertension but mechanism of abnormality is not known. In a small, randomized, crossover, placebo-controlled study, deactivation of CB chemoreceptor's by hyperoxia (respiration with 100% oxygen) attenuated the enhanced muscle sympathetic nerve activity in untreated hypertensive men, but no change was observed in controls [96]. It has also been shown that hyperoxia decreases BP acutely in patients with hypertension, but not in normotensive controls. These data point to a potential pathogenetic role of tonic chemoreceptor drive in the development of sympathetic over activity in hypertension [99]. Surgical removal of carotid body has been performed in human for reason other than hypertension (bronchial asthma, COPD). A BP fall from 170 to 130 mmHg was observed after 5 day of removal of carotid body and sustained for 6 month after bilateral carotid body surgery in hypertension patient where as no effect on BP seen in normotensive patient. To data no study addressing the effect of unilateral or bilateral carotid body resection for hypertension in human has being completed but first in man studies are ongoing.

### 5.2.4. Arteriovenous Fistula

The self expanding device creates a 4 mm AVF between iliac artery and vein, generating a sustained calibrated shunt volume 800 ml/minute within a short period of time (1 Hour). Several mechanisms are hypothesized to causes BP reduction after creation of AVF [100]. Reduction in total systemic vascular resistance, despite an increment of cardiac output is the main mechanism. Enhanced tissue oxygen delivery caused by increased arterial oxygen content may reduced peripheral and renal chemoreceptor activation and thus decrease sympathetic activity. Reduction in systemic vascular compliance and effective arterial volume may also improve arterial compliance, contributing to reduced cardiac work load, despite increased cardiac output [100]. In first randomized controlled trial of this technique at 6 month intervention group showed a reduction in office systolic BP of 27 mmHg compared with a fall of 4 mmHg in normal care group

corroborated by ambulatory BP monitoring. Expected adverse effects are induction of venous stenosis and thrombosis and development of right HF so not used commonly.

### **5.2.5. Renal artery Stenting**

Percutaneous transluminal angioplasty with Stenting for renal artery stenosis is controversial. The recent clinical trials revealed that little or no benefit for BP control, preservation of kidney function or prevention of CV or renal event with use of renal artery Stenting in hypertensive patient with renal artery stenosis [101] [102]. Angioplasty of fibromuscular lesion almost always benefits and often curative of associated hypertension and therefore recommended for treatment choice of hypertension. Poor controlled hypertension with CV risk then endovascular angioplasty with or without Stenting should be considered when drug therapy is unsuccessful. In ASTRAL trial renal artery revascularization did not result clinically relevant reduction in BP but cause high incidence of adverse procedure related complication so not used commonly.

## **6. 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  $\geq 130$  mmHg or an average diastolic BP  $\geq 80$  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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## Conflicts of Interest

We declare that none of the authors have any financial and personal relationship with other people or organizations that can inappropriately influence the quality of the work present in the manuscript.

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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.