

ABSTRACT

Change is the way of life. Everything in this universe keeps on changing, so also the best practices for hypertension keeps on changing to further optimize the results. It is important to bear in mind that the mortality in controlled hypertensive is not similar to normotensive and is at least two times greater. Therefore the treatment of hypertension should not be BP centric but disease centric policy should be employed. Fibrosis which occurs in hypertensive patients in the heart, LA, aorta and small vessels is an important contributor to morbidity and mortality. It is important to bear in mind that the office based readings of BP represents only a snapshot in time with low reproducibility. The ambulatory blood pressure monitoring provides an idea about the 24 hr BP profile. Besides this, it also gives an idea about the dipping patterns of blood pressure, the morning surges and the BP variability which has substantial prognostic and therapeutic importance. The goals of BP control are 140/90 mm Hg. The Sprint trial did show benefits of additional lowering of BP to 120 mm Hg but it is important to bear in mind that BP measurement in this trial was unique and never done before ,i.e., unattended, automated, unobstructive with patient relaxing in an AC room for 5 minutes before recording the reading. Therefore the reading of SPRINT 120 mm Hg will be higher by 10-15 mm Hg, if we record BP in the conventional manner in the clinic. Therefore lower goal of 120 mm Hg systolic of SPRINT cannot be applied in real practice as such. Among drugs used for hypertension, CTD is preferred over hydrochlorothiazide, Azilsartan a new sartan, has additional advantages and CCB Cilnidipine had additional advantage over amlodipine in that it provides renoprotection and has minimal chance of edema. Atenolol is out and currently vasodilatory betablockers are used for treatment of hypertension particularly when it is associated with coronary heart disease and heart failure. Angiotensin Receptor Nephilysin inhibitor is undergoing evaluation in hypertension with lot of excitement. Spironolactone is the fourth preferred drug in resistant hypertension. A panoply of interventional techniques including renal denervation been evaluated for treatment of hypertension but none of them have been approved for clinical use.

The last couple of years have witnessed spectacular advances in the field of hypertension, both in terms of enhanced understanding and in the availability of rich panoply of therapeutic options. Due to this, the best practices for hypertension keep on changing.

Hypertension is the biggest global cause of mortality. It is important to wear in mind that control of hypertension is not self sufficient because the mortality in a controlled hypertensive is at least two times that of normotensive. This occurs due to two reasons:

1. Hypertension is self sufficient to initiate and perpetuate atherosclerosis. This is classically illustrated in specimen of aorta of coarctation in children who usually do not have risk factors for atherosclerosis. The aorta below the coarct segment is normal but there is extensive atherosclerosis above it. Moreover atherosclerosis continues unabated even after control of blood pressure. Interestingly the HOPE-3¹ trial has shown that when candesartan is used with rosuvastatin there is a statically significant reduction in the primary end point cardiovascular death, MI and stroke compared to the group receiving candesartan alone.
2. Fibrosis develops in various parts of the cardiovascular system which has detrimental effects as mentioned below.
 - a. Fibrosis in myocardium: The fibrosis in the myocardium can be beautifully seen with Late Gadolinium Enhancement (LGE) on Cardiac Magnetic Resonance (CMR). This makes the ventricle vulnerable for development of heart failure and is also a risk factor for development of ventricular arrhythmias and sudden cardiac death.
 - b. Fibrosis in the left atrium: This predisposes for development of atrial fibrillation (AF) and stroke. This can be beautifully seen by LGE on CMR and is also utilized in conjunction with CHA₂DS₂-VASc score for prediction of stroke in AF. Moreover those patients who have left atrial fibrosis, the recurrence after Radio Frequency Ablation (RFA) for rhythm control is high. In fact, most of the electrophysiologist before attempting RFA in AF, visualize fibrosis in left atrium by CMR.
 - c. Fibrosis in the Aorta: In normal young individuals, the aorta is compliant and the aortic Pulse Wave Velocity (PWV) is about 8 meters / sec. but if there is fibrosis in the aorta, this result in decrease compliance and the aortic PWV is increased. In normal individuals the pulse wave after travelling from aorta to periphery comes back to aorta in diastole and this result in augmentation of diastolic

Table 1 : Criteria for diagnosing hypertension

Category	SBP	DBP
Office BP Criteria		
Office BP	≥ 140	≥90
Ambulatory BP Criteria		
Daytime	≥135	≥85
Nighttime	≥120	≥70
24-H	≥130	≥80
Home BP Criteria		
Home BP	≥135	≥85

blood pressure and increase in coronary filling but in aortopathy because of increase in aortic PWV, the pulse wave traverses fast from aorta to periphery and comes back to aorta in systole itself. This exerts several deleterious effects on the aorta.

- Increased central aortic systolic pressure.
- Increased LV after load.
- Increased pulsatile strain with chances of plaque rupture
- No diastolic augmentation.
- Decreased coronary perfusion.

Aortopathy is a very important predictor of future cardiovascular events in hypertension

BLOOD PRESSURE RECORDING

For several years we have been utilizing office blood pressure for diagnosis and treatment of hypertension but it is important to remember that the office based readings represent only a single snapshot in time with low reproducibility. The Ambulatory Blood Pressure Monitoring (ABPM) provides an idea about the 24 hour BP profile²⁻⁴ (Table 1).

Besides this, it also gives vital information regarding several parameters mentioned below.

Nocturnal blood pressure: Normally the blood pressure falls in the night by 10% .If it does not dip in night than it is called non dipper pattern and this is associated with increased morbidity and mortality⁵⁻⁹. There are several types of nocturnal BP patterns as mentioned in (Table 2).

The important causes of non dippers include obesity, Obstructive Sleep Apnoea (OSA), high salt intake in salt sensitive subjects, orthostatic hypotension, autonomic dysfunction, Chronic Kidney Disease (CKD), old age, diabetic neuropathy, old age etc.

- Morning surges of blood pressure:** Normally the BP starts rising 90 minutes before your expected arousal and then rise, the maximum rise being less than 35 mm Hg. If the surge is more than 35 mm Hg, this is associated with increased incidence of cardiovascular events¹⁰⁻¹².
- Blood pressure variability:** The BP variability is

Table 2: Criteria for different types of dippers

Subset	Criteria	
	Nocturnal BP fall	Night to day time BP ratio
Normal dippers	>10%	0.8 to 1
Extreme dippers	>20%	<0.8
Non dippers	No fall	>1.0
Reverse dippers	↑ BP during night	>1

defined as the average variation of BP throughout 24 hrs. quantitated as the SD of ABPM readings and is usually around 10-15 mm Hg for the day and 5-10 mm Hg for the night time. If the BP variability is increased, this is associated with increased incidence of cardiovascular events. Interestingly, the use of calcium channel blockers like amlodipine is associated with decreased cardiovascular events.

Moreover the effect of BP lowering medicines is best assessed by 24 hour ABPM¹³⁻¹⁴

Hypertension and vascular disease

Hypertension no doubt is associated with increased macrovascular disease in coronary, cerebral and peripheral arteries but what is not being realized by many that hypertension is also a very important cause of cognitive decline due to microvascular disease in the brain particularly when it is associated with diabetes.

Goals of blood pressure control:

The goals of BP are decreasing over the years (Figure). In JNC 4/5 the goal of SBP was 160, it decreased to 150 in JNC 6 and further dropped to 140 mm Hg in JNC 7. Interestingly the SPRINT trial¹⁵ showed that 120 SBP was better than 140 mm Hg .The trial showed a 25% reduction in the primary end point of MI, ACS (non-MI), stroke, heart failure or CV death, the all cause mortality and CV mortality decreased by 27 and 43 % respectively. The hospitalization for heart failure was decreased by 38%.

The SPRINT trial did show benefits of additional lowering of BP to 120 mm Hg but it is important to bear in mind that the technique of BP measurement in this trial was unique and never done before, i.e., unattended, automated, unobstructive with patient relaxing in an AC room for 5 minutes before recording the reading. Therefore the reading of SPRINT 120 mm Hg will be higher by 10-15 mm Hg, if we record BP in the conventional manner in the clinic. Therefore lower goal of 120 mm Hg of this trial cannot be applied as such in real practice

The 2016 European Guidelines on CVD prevention in clinical practice therefore has not directly endorsed SPRINT trial but it says based on current data, it may still be prudent to recommend lowering SBP/DBP to values within the range 130-139/80-85 mm Hg, and possibly close to the lower values in this range, in all hypertensive.

The SPRINT trial also has several limitations.

Table 3: Targets for blood pressure in diabetes with hypertension

Guideline	Subset	BP Goal
ACC/AHA 2014	Diabetes	<140/90
ASH/ISH 2014	Diabetes	<140/90
ESH/ESC 2013	Diabetes	<140/85
ADA 2016	Diabetes	<140/90

1. It is an open label study
2. It represents only 20% of total hypertensive population as patients with diabetes, congestive heart failure, proteinuria >1 gm/day, eGFR < 20 were excluded
3. The SPRINT trial cannot be applied to diabetics as the ACCORD BP¹⁶ and ACCORDION trial carried out in diabetic were negative
4. It cannot be applied to frail elderly.

The big question is therefore why diabetics do not benefit from intensive narrowing. Perhaps, diabetics have microvascular disease and greater BP lowering decreases perfusion pressure and increases cardiovascular events. Pre-diabetics may benefit

Effect of lowering BP in target organs

Curiously enough, different organs behave differently to decrease in BP.

- a. Brain: The dicta for brain is lower is better i.e. lower the BP, less is the incidence of stroke as shown by ACCORD BP¹⁶ and INVEST trial¹⁷.
- b. Heart: As the coronary arteries are filled in diastole, lower diastole blood pressure below 70 to 80 increases the incidence of acute myocardial infarction and this results in a J-shaped curve. Thus in patients with coronary artery disease, the blood pressure should be carefully lowered.
- c. Kidney: In kidneys, it is the intraglomerular pressure that matters more than the BP in the renal arteries. If the intraglomerular pressure is increased, this results in proteinuria which adversely affect the kidneys. Therefore in renal hypertension, drugs which decrease intraglomerular pressure like ACEI / ARBS are preferred.

Diabetes and Hypertension

The cut off point for control of blood pressure is outlined in Table 3.

The ACCORD, ACCORDION and INVEST trial failed to show that lower blood pressure is better for diabetes. The ACCORD trial showed no difference in the primary end point of MI stroke and cardiovascular death between the groups of patients with systolic blood pressure 140 vs. 120 mm Hg. The INVEST trial showed that there was a trend towards greater all cause mortality in the subset of patients with systolic blood pressure of <130 mm Hg. i.e. tight control compared to usual control i.e. blood pressure

Table 4: Targets for blood pressure in chronic kidney disease and hypertension

Guideline	Subset	BP Goal	Initial drug treatment option
ACC/AHA 2014	CKD	<140/90	ACEI/ARB
ASH/ISH 2014	CKD	<140/90	ACEI/ARB
ESH/ESC 2013	CKD no proteinuria CKD + proteinuria	<140/90 <130/90	ACEI/ARB ACEI/ARB
CHEP 2013	CKD	<140/90	ACEI/ARB

between 130-140 mm Hg. It also showed that if systolic blood pressure lowered below 120 it results in an increase in mortality.

Chronic Kidney Disease and Hypertension:

The goals of blood pressure are outlined Table-4 the cutoff point is 140/90 mm Hg. if there is proteinuria lower BP goal i.e. 130/90 is beneficial. The AASK trial¹⁸ showed no benefit in the primary outcome of progression of kidney disease in patients of CKD with hypertension but when the data was analysed on the basis of PC ratio, the subset of patient with PC ratio >0.22 showed benefit.

Drugs for treatment for hypertension

Commonly four groups of drugs are used for treatment of hypertension.

- a. Diuretics: Chlorthalidone (CTD) is preferred over hydrochlorothiazide (HCTZ) which we have been using for several decades. This is because CTD produces greater reduction in BP including nocturnal BP and is associated with decrease in the cardiovascular events (CVE). HCTZ has never been shown to reduce CVE. Indapamide is also a good diuretic with no metabolic side effects.
- b. RAAS Blockers:

There are 4 types of RAAS blockers as mentioned below :

 - i. Angiotensin Converting Enzyme Inhibitors (ACEIs): These agents although they produce incomplete RAAS inhibition but have excellent outcome data.
 - ii. Angiotensin Receptor Blockers (ARBs): Telmisartan in the ONTARGET trial was found equivalent to ACE inhibitor Rampril and is approved for clinical use like the ACEI Rampril.

Azilsartan is a new sartan and has the advantage over other sartan that besides blocking AT1 receptors, it also activates ACE2 Angiotensin (1-7) mass pathways and provides vasculoprotective and vasodilatory effects. In terms of blood pressure reduction it is therefore more potent than the other

Table 5: Ongoing trials of LCZ696 in hypertension

Trial number	Patient population	Brief title	Comparator
NCT01785472	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Asian Patients With Essential Hypertension	Olmesartan
NCT01599104	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Japanese Patients With Essential Hypertension	Olmesartan
NCT01870739	Essential hypertension	A Study to Evaluate the Effect of LCZ696 on Aortic Stiffness in Subjects With Hypertension	Olmesartan
NCT01615198	Essential hypertension	Efficacy and Safety of LCZ696 in Comparison to Olmesartan in Elderly Patients With Essential Hypertension	Olmesartan
NCT01681576	Salt-sensitive hypertension	Assessment of LCZ696 and Valsartan in Asian Patients With Salt-sensitive Hypertension	Valsartan
NCT01256411	Essential hypertension	A Long-term (12 Months) Safety, Tolerability and Efficacy Study of LCZ696 in Patients With Essential Hypertension	NA
NCT01601470	Mild-to-moderate hypertension	Evaluation of Drug-drug Interaction Between LCZ696 and Sildenafil in Subjects With Mild to Moderate Hypertension	Sildenafil
NCT01353508	Hypertension; heart failure and healthy volunteers	Sodium Excretion of LCZ696 in Patients With Hypertension; Heart Failure and Healthy Volunteers	Valsartan
NCT01692301	Hypertension	Study of the Safety and Efficacy of LCZ696 on Arterial Stiffness in Elderly Patients With Hypertension	Olmesartan, Amlodipine, Hydrochlorothiazide
NCT01663233	Essential hypertension	Efficacy and Safety of LCZ696 200 mg + Amlodipine 5 mg in Comparison With Amlodipine 5 mg in Hypertensive Patients Not Responding to Amlodipine	Amlodipine
NCT01646671	Severe hypertension	Safety and Tolerability and Efficacy of LCZ696 in Japanese Severe Hypertensive Patients	NA
NCT01631864	Hypertension, concurrent obesity	Evaluation of the Metabolic Effects of LCZ696 and Amlodipine in Obese Hypertensive Subjects	Amlodipine
ISRCTN11958993	Chronic kidney disease	Randomized multicentre pilot study of LCZ696 vs. Irbesartan in patients with chronic kidney disease: UK Heart And Renal Protection (HARP)-III	Irbesartan

sartans and provides good blood pressure control.

- iii. Direct Renal Inhibitors (DRI): These drugs despite a sound theoretical basis failed to produce outcome data in various trials and therefore they are not preferred.
- iv. Angiotensin Receptor Neprilysin Inhibitors (ARNI): This drug has already been approved for clinical use in patients with heart failure with reduce ejection fraction as Class-I (B) recommendation in various guidelines. The valsartan in ARNI produces RAAS blockade and the neprilysin inhibition with sacubtril results in increased bioavailability of natriuretic peptides, bradykinin and substance P, which produces natriuretic, vasodilatory and anti-proliferative effects.

ARNI is now being evaluated for treatment of hypertension. The PARAMETER study¹⁹ showed favourable effects. This 52-week multi-center study randomized 454 patients with hypertension aged ≥ 60 years with a mean sitting systolic blood pressure (SBP) of ≥ 150 to < 180 and a pulse pressure of > 60 mm Hg to once daily ARNI (200 mg) or olmesartan (20 mg) for four weeks, followed by a forced titration to double the initial doses for the next eight weeks. At 12–24 weeks, if the BP target had not been attained, amlodipine (2.5–5 mg) and subsequently hydrochlorothiazide (6.25–25 mg) were added. The primary and secondary endpoints were changes from baseline in central aortic systolic pressure and central aortic pulse pressure at week 12, respectively.

Results showed that after 12 weeks, patients treated with ARNI had a 3.77 mmHg greater reduction in central aortic systolic pressure and a 2.4 mm Hg greater reduction in central aortic pulse pressure from baseline compared to patients treated with olmesartan. Additionally, the 24 hour ambulatory brachial and central SBPs were significantly reduced from baseline to 12 weeks in both treatment arms, with ARNI lowering brachial SBP by an additional 4.1 mmHg and central SBP by an additional 3.3 mmHg compared to olmesartan. This finding was most pronounced during the nighttime.

In other findings, a greater percentage of patients treated with olmesartan (47 percent) required additional hypertension medication at weeks 12–24 compared to patients in the ARNI group (32 percent). Investigators also noted that an exploratory analysis of the carotid-to-femoral pulse wave velocity indicated a trend toward greater improvement in a subgroup of ARNI treated patients with the stiffest arteries at baseline.

PARAMETER is the first randomized study demonstrating the ability of ARNI to significantly reduce central blood pressure and pulse pressure compared to an ARB in high-risk older patients with systolic hypertension and a wide pulse pressure.

These data are important because lowering systolic and pulse pressure in older people with stiffened arteries is an unmet need in our endeavor to reduce the risk of cardiovascular disease and heart failure in older people. The results suggest that ARNI has been able to achieve more in this regard than existing treatments and indeed this is an exciting advance.

The holy grail of systolic hypertension therapy is to achieve a 'destiffening' effect. The fact that release of BNP was reduced for ARNI provides indirect evidence that this may be occurring. Currently studies are under way using MRI to directly measure changes in arterial distensibility following ARNI treatment.

Although ARNI has shown impressive reduction in systolic and diastolic blood pressure, the long-term antihypertensive efficacy of ARNI has not been fully evaluated. Moreover the effect of ARNI on cardiovascular outcomes in patients with hypertension is unknown. It is also to be seen whether ARNI also confers long-term prognostic benefits in patients with hypertension. Further studies need to be conducted to elucidate the role of ARNI in hypertensive patients with (i) diabetes, (ii) chronic kidney disease (iii) elderly (iv) resistant hypertension. Since blacks were underrepresented in the published hypertension trials, future trials should also include adequate black population. Most importantly, studies need to be conducted comparing antihypertensive efficacy and outcome of ARNI with other drug classes such as ARBs, calcium-channel blockers and diuretics.

Besides PARAMETER trial, several other clinical trials are ongoing (Table 5).

- c. Calcium channel blockers (CCBs): Amlodipine is a time tested CCB for treatment of hypertension and has been tested in several large scale trials with beneficial results. But the the main problem with amlodipine is pedal edema. Of late the fourth generation CCB is now commercially available. It has the advantage that it not only acts on the L-type calcium channel blockers but also blocks the N-type calcium channels which suppresses excess norepinephrine release from the sympathetic nerve endings. This provides cardio-protection²⁰ as it does not increase heart rate and cardiac contraction and also provide renal protection by decreasing proteinuria²¹. It also produces venodilation and decreases chances of pedal edema²².
- d. Beta blockers: For several years beta blockers like atenolol has been commonly used for treatment of hypertension but the meta analysis by Carlberg²³ showed that it increases all cause mortality and CV mortality by 13% and 16%. It increased MI by 17% and curiously enough the strokes were increased by 30%. As a result the NICE guidelines

for hypertension in 2011 degraded beta blockers to number four. Currently vasodilatory beta blockers like Nebivolol, carvedilol are used for treatment of hypertension. This has minimal side effects but long terms trials are lacking with these agents are lacking.

Combination Therapy

Most patient of hypertension in the long run requires combination therapy²⁴. The desirable combinations are ACEI / ARB + Diuretics, CCB + Diuretics, ACEI / ARB + CCB, ACE / ARB + CCB +Diuretics.

Resistant hypertension

Hypertension uncontrolled (>140/90 mm hg) with triple combination i.e., ACEI/ARB +CCB + CTD is categorized as resistant hypertension.

Depending on the population examined and the level of medical screening, the prevalence of resistant hypertension has been reported to range from 5–30% of the overall hypertensive population, with figures less than 10% probably representing the true prevalence. Resistant hypertension is associated with a high risk of CV and renal events²⁵⁻²⁸.

But before labeling somebody as resistant hypertension, one should rule out the possibility of apparently difficult to control hypertension due to inappropriate cuff size, pseudohypertension, non-adherence to drug therapy, unknowingly taking large amount of salt, inadequately prescribed dosage or improper combination, white coat hypertension, drug induced hypertension etc. if true resistant hypertension is present, one should exclude obstructive sleep apnoea (OSA), hypothyroidism, renovascular hypertension, primary aldosteronism, aortoarteritis, endocrinal hypertension etc.

What should be the fourth drug if blood pressure is not controlled with ACE/ARB, CCB/Chlorthalidone i.e. resistant hypertension ?

This was tested in the PATHWAY 2 trial²⁹ which showed that spironolactone was distinctly superior to bisoprolol and doxazosin and therefore this should be the fourth drug of choice.

Other drugs that can be used include betablockers like nebivolol or bisoprolol, alpha blockers, like prazosin ,direct vasodilators like hydralazine, minoxidil, centrally acting drugs like clonidine, moxonidine etc

Interventional therapy in hypertension

Several interventions have been used for treatment of hypertension like carotid baroreflex activation, Iliac AV anastomosis and renal sympathetic denervation.

- Baroreflex activation: It decrease blood pressure by vagal stimulation but the problem with this technique is that carotid stenosis is seen about 60% of patients and we do not know how to prevent it ?
- Iliac AV anastomosis: In this external iliac artery connected to external iliac vein by a device. It decreases blood pressure by decreasing vascular

resistance. This is associated with venous stenosis in 25% of patients but this can be treated by venodilatation.

- Renal sympathetic Denervation: This was a very promising technique and the initial results with SYMPLICITY-1 and 2 were exciting but distressingly enough the SIMPLICITY HTN-3 trial³⁰ although it met the safety end point, it failed to show any reduction in blood pressure compared to the Sham control group. Therefore it has not been approved for clinical use. The failure of the trials was attributed to several reasons like operator inexperience / failure, fault with the catheter and patient in the late stage of disease with burnt out sympathetic activity. The problem with the technique is that there is no parameter to document success of renal denervation/ technical failure. New improved catheters for the procedure are being designed with circumferential denervation of renal artery and its branches and the initial result are exciting. It seems renal sympathetic denervation is still alive and not dead and may bounce back in future.

But we should not forget that the major battle for hypertension is to be fought outside the clinics and hospitals because the major chunk of hypertensive patients is still out of reach. This can never be done merely by the medical fraternity but requires cohesive efforts by the government, voluntary agencies, paramedical workers, electronic and print media etc.

SUMMARY

Hypertension is the commonest cause of cardiovascular morbidity and mortality throughout the globe including our country. Prevention should be the goal and indeed it is possible. For hypertensive patients, we have panoply of powerful antihypertensive drugs to control it. But for optimum treatment, a disease centric approach should be employed rather than merely a BP centric approach.

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