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# A Difficult Case of Resistant Hypertension

Dilip A Kirpalani<sup>1</sup>

## ABSTRACT

A 38 year old male suffering from Essential Hypertension, was initially labelled as Resistant Hypertension but investigations revealed that he had “Apparent” Resistance and not “True” Resistance. We initially managed, as per the protocol outlined herein, to rule out “Apparent” Resistance. We suitably adjusted his therapy and lifestyle to bring his blood pressure under control with 3 drugs. One and half years later, he returned to Hypertension Clinic labelled as “Resistant” Hypertension once again. This time however, investigations confirmed “True” Resistance. The appropriate line of investigation and management now required is outlined herein. The blood pressure could only be brought under control after adding a Mineralocorticoid Receptor Antagonist (MRA), Eplerenone. The results of the PATHWAY-2 Trial suggest that the addition of one of the MRA group of drugs should be the first choice in the management of “True” Resistant Hypertension in a case of Essential Hypertension.

Resistant Hypertension is defined as uncontrolled blood pressure (target not achieved) in a patient who is on optimal doses of 3 antihypertensive medications, one of which is a diuretic.<sup>1</sup> Adequate BP control achieved in a patient with optimal doses of 4 or more antihypertensive medications is also Resistant Hypertension.

A 38-year-old male, hypertensive since 3 years, 174 cm tall and weighing 87 kg was referred to us for ‘Resistant Hypertension’. He was a non-diabetic, not aware of any obvious kidney disease, had a history of childhood asthma and gave a history of weight gain of 10 kg over the last 3 years. He was on 3 medica-

tions for his Hypertension – Amlodipine 5 mg once daily, Metoprolol 25 mg twice a day and Hydrochlorothiazide 12.5 mg once daily.

He gave history of recurrent nose blocks in the mornings for which he regularly consumed nasal decongestant drops. His wife gave a history that he snores and described typical apnoeic spells during his sleep, suggestive of Obstructive Sleep Apnoea.

On clinical examination, his pulse was 84 beats per minute, regular and BP by Hg Manometer was 160/105 mmHg. However, when resting BP was taken, by Omron HEM 907 machine (machine used in SPRINT Trial) by a paramedic, it was 140/95. Systemic examination was normal except for pedal oedema; patient was on Amlodipine.

Now, in any case of ‘Resistant Hypertension’,

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it is first important to rule out White Coat Hypertension and causes of 'Apparent' drug resistance, before labelling the patient as 'True Drug Resistant'.<sup>2</sup> Causes of 'Apparent' drug resistance in a hypertensive could be due to the following:

1. Cuff-related artefact
2. Patient non-adherence (non-compliance with medications and/or dietary salt restriction)
3. Physician non-adherence which would be due to use of inappropriate combination of antihypertensives, use of suboptimal doses of antihypertensives or adhering to a wrong target in a particular patient.

In our patient, referred to us for 'Resistant Hypertension', we did an Ambulatory BP Monitoring, which confirmed uncontrolled Hypertension during day and night and also ruled out any White Coat effect. A Polysomnography done on him also confirmed the presence of Obstructive Sleep Apnoea, for which he was started on C.P.A.P.

An analysis of his antihypertensive prescription showed that there was no Renin Angiotensin Blocker. In addition, this patient was on a beta blocker which is not a frontline drug in the management of Uncomplicated Hypertension today. This was a case of Uncomplicated Hypertension whose renal functions on investigating were normal, urine sediment bland and ECG and Echo showed a normal ejection fraction with the left ventricle hypertrophy, but no other abnormalities.

Hence, we modified his prescription. Beta Blocker was stopped. Olmesartan 40 mg once daily was added, Hydrochlorothiazide was replaced by Chlorthalidone 6.25 mg once daily and Amlodipine was increased to 10 mg daily.

Within 4 weeks of making these changes, the patient had reached a target BP of 135/85 mmHg and 125/78 on Omron HEM 907. Hence, this was not a case of True Resistant Hypertension but a case of 'Apparent' Drug Resistance due to an inappropriate combination of antihypertensive drugs: the patient's

blood pressure came under control when the drug combination and doses were appropriately modified.

However, he was then lost to follow-up and returned one and a half years later on the same drug combination but with uncontrolled blood pressures at home and in the clinic. At this point of time, we checked for dietary salt compliance and medication compliance, which were both good. 24-hour urinary sodium is a good test for checking dietary salt compliance in a person who has normal GFR.

We also ruled out White Coat Hypertension with an Ambulatory BP monitor and having done that we suspected True Resistant Hypertension. Hence, we investigated for Secondary Hypertension. We ruled out renal, adrenal, and thyroid causes of Secondary Hypertension. This was now a case of True Drug Resistance in a patient with Essential Hypertension.

This patient was clinically not showing any signs of fluid overload, nor was he taking any drug that could be inadvertently raising his BP (earlier, he had been on nasal decongestant drops but he had stopped using these since last seven months). Volume overload and drugs causing hypertension are two very important causes of resistance to antihypertensive drugs in a patient with Essential Hypertension.<sup>3</sup>

His clinic BP was 140/110 mmHg by Hg manometer and 140/100 by Oscilometric technique (Omron HEM 907) and he was on Olmesartan 40 mg once daily, Amlodipine 10 mg twice a day and Chlorthalidone 12.5 mg once daily.

At this point, we added Moxonidine 0.3 mg twice a day to his current prescription, but to no avail. Two weeks after adding Moxonidine, we added a fifth drug. This was a Mineralocorticoid Receptor Antagonist, Eplerenone.<sup>4</sup> We preferred Eplerenone to Spironolactone in order to avoid Gynecomastia and the patient could afford a more expensive drug, namely Eplerenone.

With 50 mg Eplerenone daily along with previously mentioned doses of Amlodipine,

Chlorthalidone, Olmesartan & Moxonidine (i.e., 5 drugs combination), he returned with a home BP chart showing well-controlled blood pressures and an oscillometric BP in the office of 128/74. He had a serum Creatinine of 1 mg/dL and serum Potassium of 3.9 mEq/L.

In summary, this was a patient with Essential Hypertension, who previously had 'Apparent' drug resistance to antihypertensives and came under good control with modification to an appropriate antihypertensive regimen; later, this patient developed True Resistant Hypertension, which ultimately got controlled with 5 antihypertensive drugs. This patient is now on a regular follow up with us and by definition, is a difficult case of Resistant Hypertension as it took 5 antihypertensive agents to bring his BP under control including Chlorthalidone, an Angiotensin Receptor Blocker, a Mineralocorticoid Receptor Antagonist, a centrally acting Presynaptic Alpha-2 agonist and a Dihydropyridine

Calcium Channel Blocker.

Such patients, as the one presented above, constitute about 10% of hypertensive patients in general practice and about 30% or more of the hypertensive patients presenting to a Hypertension Specialist's Clinic.

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# A Descriptive Observational Retrospective Study to Assess the Presence of Hyperuricemia in Indian Population

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## ABSTRACT

**Objective:** A descriptive observational retrospective study was conducted on Indian populations to estimate the presence and burden of hyperuricemia across various states.

**Methodology:** The 87,583 patients between  $\geq 20$  and 80+ years age adults, who underwent screening of serum uric acid levels in diagnostic labs across India between 2016 and 2017 were studied. SUA cut off was taken as  $>7$  mg/dL for men and  $>6.0$  mg/dL for women.

**Results:** In total patients, the proportion of males (50.57%) and females (49.43%) was nearly equal. The overall prevalence in females and males were 20.2% ( $\pm 95\%$  CI, 19.83 – 20.57) and 21.5% ( $\pm 95\%$  CI, 21.11 – 21.89), respectively. Overall, females have shown increase in prevalence with age. Among males, prevalence is maximum at age group 30-40 and trend is slightly declining and consistent with age.

**Conclusions:** The results were comparable with previous literature and the overall presence of the disease is significant. The study also suggested the emerging hyperuricemia burden on post-menopausal women and young adults, which needs an immediate attention.

## INTRODUCTION

Uric acid is the end product of purine

catabolism, excreted by the kidney and intestine. Under normal circumstances, its production and excretion maintain a fine balance. Any imbalance can result in hyperuricemia, a potentially harmful condition leading to its deposition in tissues and joints. Hyperuricemia is usually associated with an unhealthy lifestyle such as imbalanced diet exceeding in purine nucleotides and certain medications like diuretics.

Hyperuricemia is implicated in various

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complications such as gout, nephrolithiasis, hypertension, metabolic syndrome and cardiovascular conditions. All these associated complications suggest that hyperuricemia takes an enormous toll not only on the health but also on economy of a country. A study by Wertheimer et al., estimates the cost of gout alone to the USA is more than \$6 billion by affecting 8 million Americans whereas such data on Indian population is not available.<sup>1</sup> Considering the wider impact of hyperuricemia with related conditions, the overall cost incurred in the management of hyperuricemia and associated conditions will be even higher.

Various population-based studies have suggested that the prevalence of hyperuricemia was 15-20%, and uric acid deposition in 4% cases.<sup>2-5</sup> Studies in India have shown high prevalence of hyperuricemia in high risk groups like diabetic patients (~25%).<sup>6</sup> However, such research and information on population-based studies in India are still inadequate.

In the current study, we have estimated the presence of hyperuricemia in India by extrapolating findings of real-world data from diagnostic labs across multiple Indian states and regions. The objective is to estimate the overall prevalence of hyperuricemia across various populations and states alongside the burden of hyperuricemia in India.

## MATERIALS AND METHODS

A descriptive retrospective study was conducted based on diagnostic lab data i.e. secondary data was considered for research purpose. Confidentiality of subjects was maintained by removing the personal identifying information of the data used in the analysis.<sup>7</sup> An overall patient data of 87,583 from  $\geq 20$  years to 80+ years age adults, who underwent screening of serum uric acid levels (SUA), was analysed. The data was collected from seven states, including Delhi (DL), Andhra Pradesh (AP), Maharashtra (MH), Punjab (PB), Tamil Nadu (TN), Uttar Pradesh (UP) and West Bengal (WB) from year

2016-2017. These visits include preventive package, routine tests, and tests done for diagnosis of hyperuricemia on suggestion of doctor. As the study is based on anonymized retrospective secondary data, any formal ethics committee approval and informed consent were not required and hence not taken.

## Statistical Analysis

There were no specific inclusive criteria other than the above considered for the analysis. Data analysis was done by using SQL programming, R-statistical tool version 3.5.3, and Microsoft excel 2016. The results are presented in the form of proportions.

Hyperuricemia is defined as a serum urate concentration  $>405 \mu\text{mol/L}$  ( $>6.8 \text{ mg/dL}$ ). However, there are no unified cut off values to define the disease, also, in presence of any comorbidities like, hypertension, cardiovascular disease and gout, use of rather stringent cut offs ( $>6.0 \text{ mg/dL}$ ) were suggested.<sup>5,8-11</sup> In the current study, hyperuricemia was defined if SUA concentration was  $>7.0 \text{ mg/dL}$  ( $415 \mu\text{mol/L}$ ) in men or  $>5.7 \text{ mg/dL}$  ( $340 \mu\text{mol/L}$ ) in women.<sup>12a</sup>

We have considered the same methodology that was used by Billa et al., 2018 (with minor changes as per the data requirements) in the current study.<sup>12b</sup> To calculate state wise burden of hyperuricemia, the lab findings were considered as the corresponding state hyperuricemia population of adults. The weighted prevalence of hyperuricemia for the state was calculated in the following way -

1. Initially, the prevalence of hyperuricemia was estimated in different age and gender categories by applying SUA criteria mentioned above.
2. The fraction of population of respective state in different age and gender categories was then obtained as per census 2011 ( $\geq 20$  years age).
3. Next, the prevalence of hyperuricemia in each age and gender category of that state was computed using prevalence patterns

of the sample population.

4. Lastly, the overall prevalence for the state was estimated by taking weighted average of prevalence in all age and gender categories of that state.

The above parameters were represented in proportions with 95% confidence interval.

## RESULTS

In a total of 87,583 patients, the overall proportions of males (50.57%) and females (49.43%) were nearly equal (Table 1). Samples from MH (42.6%) make up a large fraction of the total, followed by DL (23.3%) and smallest in UP (3.15%) (Table 1). Amongst the sample, 20-30 and >80 years age category was relatively less in proportion when compared to other age categories, 7.88% and 4.11%, respectively (Table 2). The middle to old age groups, 40-70 years, have 60% contribution in combine (Table 2).

The overall percentage was 20.9% ( $\pm 95\%$  CI, 20.63-21.17) in a range of 18.7-23.8% across

states and 17.0-29.7% in age groups (Table 3 and 4). The prevalence in females and males varies from 12.2 to 39.5% and 18.0 to 24.9%, respectively (Table 3). The four states, DL, MH, UP and WB have prevalence >20%. The states TN (19.7%) and AP (18.7%) have comparatively lower prevalence, while PB (17.7%) has lowest prevalence.

The overall prevalence between female and male was almost comparable, 20.2% and 21.5%, respectively (Table 3). Females have shown increase in prevalence with age wherein transition from fifth to sixth decade, there is a sharp increase, ~11% (Table 3 and Figure 1). The percentage of increase from 4<sup>th</sup> to 5<sup>th</sup>, 5<sup>th</sup> to 6<sup>th</sup>, 6<sup>th</sup> to 7<sup>th</sup> and 7<sup>th</sup> to 8<sup>th</sup> decades are 4.7, 11.6, 6.6 and 2.9, respectively. Among males, prevalence is maximum at age group 30-40 and trend is slightly declining and consistent after eight decade of life (Table 3). Interestingly, the gender gap altered with age significantly from 6<sup>th</sup> to 9<sup>th</sup> decade (Figure 1). The difference between female and male from 3<sup>rd</sup> decade (-9.6), 4<sup>th</sup> (-11.6), 5<sup>th</sup> (-4.1), 6<sup>th</sup> (10.0),

**Table 1: State wise distribution of male and female population**

S. No	States	Male (%)	Female (%)	Total (%)
1	AP	4.4	3.1	6590 (7.5)
2	DL	12.8	10.5	20419 (23.3)
3	MH	19.9	22.6	37332 (42.6)
4	PB	3.1	3.2	5495 (6.3)
5	TN	3.1	2.4	4845 (5.5)
6	UP	1.5	1.7	2762 (3.1)
7	WB	5.7	5.8	10140 (11.6)
Total		50.57%	49.43%	87583 (100%)

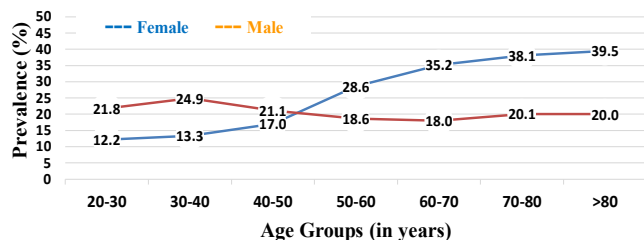
**Table 2: Age and gender wise distribution of male and female population**

S. No.	Age (Years)	Male (%)	Female (%)	Total n (%)
1	20 – 30	4.03	3.86	6905 (7.9)
2	30 – 40	8.71	8.16	14771 (16.9)
3	40 – 50	10.65	9.54	17677 (20.2)
4	50 – 60	10.32	10.97	18647 (21.3)
5	60 – 70	9.44	9.73	16785 (19.2)
6	70 – 80	5.28	5.22	9196 (10.5)
7	>80	2.15	1.96	3602 (4.1)
Total		50.57%	49.43%	87583 (100%)

**Table 3: State, age and gender wise hyperuricemia prevalence, P (%) with 95% CI**

S. #	States	P*	95% CI	Age groups (in years)	Female	95% CI	Male	95% CI
1	AP	18.7	17.7-19.6	20-30	12.2	11.1-13.3	21.8	20.4-23.2
2	DL	20.7	20.1-21.3	30-40	13.3	12.5-14.1	24.9	23.9-25.9
3	MH	21.1	20.7-21.5	40-50	17.0	16.2-17.8	21.1	20.2-21.9
4	PB	17.7	16.7-18.7	50-60	28.6	27.7-29.5	18.6	17.8-19.4
5	TN	19.7	18.6-20.8	60-70	35.2	34.2-36.2	18.0	17.2-18.8
6	UP	21.1	19.6-22.6	70-80	38.1	36.7-39.5	20.1	18.9-21.3
7	WB	23.8	22.9-24.6	>80	39.5	37.3-41.7	20.0	18.1-21.9
Total		20.9	20.6-21.2	-	20.2	19.8-20.6	21.5	21.1-21.9

\*P – Prevalence; P-value <0.001



**Fig. 1: Trends of prevalence in female and male population across age groups**

7<sup>th</sup> (17.2), 8<sup>th</sup> (18.0) and 9<sup>th</sup> decade of life (19.5). This phenomenon was very well highlighted by our study which is also in consistent with the literature.<sup>12</sup>

## Burden

The WB, MH, UP and DL are the top four states which showed relatively high burden followed by TN and PB. The onset of burden in females from 40 years age and reaches maximum at 60 years and thereafter percentage of change was consistent. While, in case of males, the burden was maximum at 30-40 years age and declines thereafter.

## DISCUSSION

Various community level studies reported very high prevalence of hyperuricemia across world and particularly in Asia, albeit very few studies have nation-wide coverage. In India, to our knowledge, no study yet gives any insight into the overall burden. Our study offers detailed information about hyperuricemia burden across states, age and gender.

Recent studies have established association of hyperuricemia with cardiovascular (CVD) and chronic kidney diseases (CKD) also as an independent factor for hypertension (HTN).<sup>13</sup> These diseases have been reported to be one of the major contributors, CVD - 17.8% and CKD - 2.4% of morbidity and mortality in India and burdening resources in a financially constrained health system.<sup>14</sup> It is pertinent to understand the epidemiology of hyperuricemia in India, nonetheless, overall research is limited to a few regional small-scale studies lacking country-wide data. In this study, we estimated overall state wise prevalence of

hyperuricemia by extrapolating results of lab tests done at various diagnostic labs. This information in turn would help in understanding regional as well as age and gender wise trends of this problem.

The gender-based prevalence between male and female are closely comparable, 21.5 and 20.2%, respectively, which are in line with the studies conducted before at the community level.<sup>15-18</sup> A study conducted in Mizoram estimated overall prevalence as 21.4%, with higher rate in males (37.3%) than females (22.6%).<sup>15</sup> Conen et al., found prevalence among men was 35.4 and 8.2% among females in developing countries.<sup>16</sup> Zhu et al., has estimated prevalence as 21.2 and 21.6% for males and females, respectively in USA, using survey data of NHANES, from year 2007 to 2008.<sup>17</sup> A systematic meta-analysis estimated a pooled prevalence of 13.3% (95% CI: 11.9-14.6) in China.<sup>18</sup>

## Prevalence patterns among high risk categories

The SUA cut off values vary every so often with type and presence of comorbidities, for example, onset of CVD has been reported to increase with SUA levels of 6.2 mg/dL, in males and 4.6 mg/dL, in females.<sup>19</sup> Similarly, prevalence of HTN increases by 1.2 fold with increase of 1 mg/dL,<sup>20</sup> onset of cerebral disease increased with >6.0 mg/dL in both male and female,<sup>8</sup> CKD risk increased twice from 7.0 to 8.9 mg/dL and tripled with >9.0 mg/dL,<sup>21</sup> and onset of gout was reported with SUL level crossing >5-6 mg/dL.<sup>22</sup> Other than above, hyperuricemia has also been reported to have a significant association with obesity.<sup>23</sup> Rise in prevalence has been observed with increase in BMI,<sup>23</sup> 34% with BMI range 28-35 kg/m<sup>2</sup> and 47% with BMI >35 kg/m<sup>2</sup>. The ethnicity and use of diuretics are the other important factors which can have substantial influence on the SUA levels.<sup>24</sup>

The higher mean SUAs among post-menopausal women induce higher hyperuricemia incidences.<sup>25</sup> Our study consolidates this finding wherein women have shown

sharp increase, particularly, from fifth to sixth decade, with 11% (Table 3 and Figure 1). The prevalence reaching highest at 5<sup>th</sup> to 6<sup>th</sup> followed by 6<sup>th</sup> to 7<sup>th</sup> and thereafter the rate of increase declines (Figure 1). Our study reported a relation between prevalence in females with menopause age and the observations are in line with the literature. A cross-sectional study conducted in Korea has been reported that the prevalence of hyperuricemia significantly increased from the menopausal stage of late transition, independent of potential confounders.<sup>10</sup> A community-based study has been reported that there was a steady increase in SUA in females from fourth to seventh decades of life.<sup>10</sup> A study on US women indicate that the menopause was independently associated with higher SUA.<sup>26</sup> Another study on same data reported that the aging but not menopause was the reason for increased prevalence in aged women.<sup>27</sup> Multiple studies infer that the increase in SUA in females has been associated with menopause age which in turn attributed to lower reproductive hormones and subsequent decrease in renal tubular excretion of uric acid.<sup>28</sup>

In case of males, highest average prevalence was in fourth decade of life (24.9%), consistently decreasing afterwards (Figure 1). The potential risks and possible reasons have well been explained by Cao et al., that increased SUA along with BMI were found as risk factors for gonadal dysfunction in males.<sup>29</sup> Also, increase in SUA was associated significantly with decreased levels of testosterone.<sup>29</sup>

## Burden

In general, the burden of a disease is estimated in terms of financial, morbidity-mortality, quality of life, etc. The economic aspect is out of the purview of the present study. Other than common factors like obesity, diabetes, hypertension and dyslipidemia, the reported significant risk factors for hyperuricemia in males are alcohol and smoking, whereas in females, menopause.<sup>13</sup> Reportedly, 29% of the Indian male consume alcohol wherein, 31.2%

in 20-34 age group and 36.8% in 35-49, i.e. third to fifth decade of life.<sup>30</sup> This might be one of the added risk factors for the observed highest average prevalence in males in fourth decade of age. While, change in hormonal balance coupled to menopause age of females have well aligned with the observed female trends in our study.<sup>10,26-28</sup> Nonetheless, the presence of comorbidities may well add on risk factor to the reported hyperuricemia burden.

## Limitations

There are a few limitations of our study, such as, the data has been pooled from diagnostic labs and they were considered as the corresponding state level hyperuricemia population of adults. Patients visiting for labs may be different than the general population and hence extrapolation may be limited, though we have also included general wellness checks and annual checks which may make it more generalizable. Also, unavailability of risk factors information (like BMI, HTN, CKD, heart disease, medication information etc) and sample (clinical) profile makes extrapolation rather difficult over general community and thus, the prevalence might perhaps overestimate.

## CONCLUSION

The obtained results are comparable with previous literature and the resultant overall prevalence is significant. The community surveys indeed provide insights about hyperuricemia prevalence in high risk categories like obese and hypertension. The emerging trends in young male adults and post-menopausal women are high and need attention. Early screening for certain section of populations like women after 5<sup>th</sup> decade and young male adults after 4<sup>th</sup> decade is warranted. As hyperuricemia is often associated with serious comorbidities (Gout, CVD, CKD, etc), the timely screening and management may reduce mortality and improve quality of life. However, further comprehensive longitudinal studies and randomized interventional

studies need to be conducted to ascertain this hypothesis.

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# Validation of BP Monitoring Devices

Viraj R Suvarna<sup>1</sup>, Reshma Susan Reji<sup>1</sup>, Manoj A Suva<sup>1</sup>

## ABSTRACT

Hypertension is a multifactorial disease involving interactions among genetic, environmental, demographic, vascular and neuroendocrine factors. However hypertension management (diagnosis and treatment) begins with accurate measurement and diagnosis of blood pressure. There are multiple devices available in the market which helps in blood pressure measurement, such as mercury, aneroid or oscillometric. Although mercury sphygmomanometer is the gold standard, doctors need to move away from use of mercury BP measuring devices, as mercury poses a grave environmental hazard. Aneroid devices need to be calibrated from time to time; else one could get falsely accurate readings. Hence, this article aims to discuss the need for validated digital or automated oscillometric algorithm based BP monitoring devices. Validation of BP measuring devices began with a series of ad-hoc validation protocols in the 1980s. Validation is a clinical test according to a defined protocol to determine the accuracy of the blood pressure monitor; a real patient study. Calibration means checking the mercury and aneroid BP devices for accuracy and adapting the device. Automated devices are checked for accuracy and there is very rarely a need for adaptation; these devices generally work or do not, in the latter case they provide an error. To conclude, it is high time we use automated or digital oscillometric validated algorithm based devices that are environmentally friendly and cost-effective. The doctors should insist that patients should opt for such validated home blood pressure monitoring devices or BP meters, just as some have glucometers, thermometers and peak flow meters.

## INTRODUCTION

Unless it can be measured right, it cannot be managed right, so said management guru, Peter Drucker. In the world of hypertension this is apt as hypertension management (diagnosis and treatment) begins with accurate measurement and then diagnosis.<sup>1</sup>

Of course hypertension is not only about

numbers and one also needs to look at risk factors, hypertension-mediated organ damage, and concomitant illnesses (e.g., diabetes where the goal is lower than the usual < 140/90 mm Hg, or hypertension with renal disease and proteinuria where the goal is < 125/75 mm Hg).<sup>2</sup>

But the sine qua non of hypertension management is the ability to make an accurate diagnosis of hypertension in the first place.

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And this has to start with use of an accurate BP measurement device, be it mercury, aneroid or oscillometric. Since December 2017, the government has banned the use of mercury in instruments such as the thermometer, sphygmomanometer, and hence although it is the gold standard, doctors need to move away from use of mercury BP measuring devices, as mercury poses a grave environmental hazard.<sup>3</sup> An automated electronic sphygmomanometer may be an option, where there is no mercury column, but otherwise works on the same principle.

Aneroid devices need to be calibrated from time to time, else one could get falsely accurate readings, and by the time one realizes that the readings are fallacious,<sup>4</sup> it might be too late (they work on a spring mechanism like in a watch, so till you realize your watch is showing the wrong time, you will not know). Hence the need for digital or automated oscillometric algorithm based devices, but which need to be validated. So what really is the difference between calibration and validation? Personal communication with Dr. Willem Verberk, an expert on hypertension from the Cardiovascular Research Institute, Maastricht (CARIM), Netherlands, reveals that:

- Validation is a clinical test according to a defined protocol to determine the accuracy of the blood pressure monitor; a real patient study [for International Standards Organization (ISO)/Association for the Advancement of Medical Instrumentation (AAMI) in the US - 85 patients]<sup>5</sup>
- Calibration means checking the mercury and aneroid BP devices for accuracy and adapting the device, if needed; mostly the problem is that the devices do not start at zero<sup>6</sup>
- Automated devices are checked for accuracy and there is very rarely a need for adaptation; these devices generally work or do not, in the latter case they provide an error

Another interesting point is the meaning of the words, precision and accuracy. Precision

refers to reproducibility, but in the case of BP measuring devices, one may be precisely wrong every time if the device has not been validated.

So what exactly is meant by validation, and how is it done? Many societies have their international or standard protocols for validation, e.g., AAMI, ISO, British Hypertension Society (BHS) (<http://www.bhsoc.org/default.stm>), Deutsche Hypertension League (DHL), European Society of Hypertension (ESH), and Dabl Educational Trust (<http://www.dableducational.org>).

A binaural stethoscope is used. Two observers independently record data from the reference device. Each observer is unaware of the reading obtained by the other observer or test device. A minimum of 33 (ESH), 85/86 (BHS/AAMI) or 96 (DHL) patients need to be tested per the protocol of the respective medical society.<sup>7</sup> At least three valid BP recordings are done for each subject/participant, so if 85 is the sample size number, then 255 such paired BP determinations will be made available for this study.<sup>8</sup> For the BHS, these readings need to be within 5 mm Hg of the reference gold standard in 50% of cases, and 10 mm Hg in 75% of cases. Per AAMI, it should be within 5 mm Hg of the reference standard with a standard deviation of not more than 8 mm Hg.<sup>9</sup>

So when one clinically validates BP measurement devices, one has to consider the number of patients in the validation study, the kind of patients who will be measured with the device, did the device pass a validation for a special patient group, preferably one in the high BP range and one in the low BP range?, and does the cuff size range cover the need and has this been clinically investigated? Basic validation is performed on a group of subjects that is representative of an "average population without any diagnosed pre-existing conditions".<sup>5</sup> The larger the number of subjects, the more statistically significant, thus more reliable, the validation test.

Another very important fact for oscillometric



algorithm based devices is that the validation needs to be done not only for plain vanilla hypertensive patients. The measurement depends on how stiff the artery is and this determines the reflected wave.<sup>10</sup> Since it is based on a pulse waveform analysis and arterial stiffness can vary if the hypertensive patient also has, e.g., diabetes, diabetic kidney disease (CKD, all the way up to end stage renal disease), atrial fibrillation, etc., one has to validate the device for all these concomitant conditions. The Microlife device [available in India under the brand name Circa from Eris Lifesciences Limited in 3 models, viz., Practo (Rs 2600), Exclusio (Rs 5500), Premier (Rs 8000)] has been validated in 11 such conditions, viz., ESRD/those on dialysis, diabetes, elderly, children and adolescents, atrial fibrillation, different cuff sizes in the overweight/obese, pregnant women, pre-eclampsia, and hypotension. <http://www.dablededucational.org>; <http://www.bhsoc.org/default.stm>.

The Omron device is the next most validated device (7 conditions) but it needs a different device for each of those 7 conditions. Hence it can be cumbersome. Interestingly, the Omron device was used in the SPRINT study, based on which the AHA/ASH lowered their hypertension goal from < 140/90 mm Hg to < 130/80 mm Hg, but since it was not validated for diabetic hypertensives, diabetics were excluded from the SPRINT study.<sup>11</sup> Interestingly, the study was about systolic BP measurements, but there is a paper which concluded that the Omron HEM-907 XL device in patients with non-dialytic CKD appears to be accurate for measuring DBP but did not perform as well for measuring SBP.<sup>12</sup> Au contraire, the Microlife device has been shown to be accurate in measuring both SBP and DBP.<sup>13</sup> The Microlife device has been validated also in central aortic BP measurement, ankle-brachial index, and inflation mode technology, and the wrist device is being tested, though one needs to be cautious as watch straps acting as BP measuring cuffs may not be validated.<sup>14,15,16</sup> In the arm, it is the brachial artery compressed against a bone but in the wrist the compress-

ibility may not be as clear and one has the radial and ulnar arteries.

In terms of how has the Microlife device been tested in its ability to detect atrial fibrillation as a screening tool, the procedure is as follows:<sup>17</sup> it measures the last 10 pulse intervals (during deflation), it calculates mean and standard deviation (SD) of the intervals, each of the 10 intervals that is 25% longer or 25% shorter than mean time interval is discarded, the remaining is used to calculate the irregularity index (SD/mean of intervals), if irregularity index is > 0.06, an AF symbol is displayed, and the patient needs to visit a cardiologist for definitive confirmation (using ECG, Holter monitoring, event loop recorders). Overall, the sensitivity of the Microlife device is 98%, and the specificity is 92%. The Microlife device has been validated and certified by all the medical societies that are responsible for validation of BP measuring devices, and the studies have been published as well.

The algorithm of an oscillometric envelope is based on the fact that as the cuff deflates, oscillatory waves are superimposed on the blood pressure measurement. This generates an OWE (Oscillometric Waveform Envelope).<sup>18</sup> We owe it to ourselves and our patients to see to it that the device that we use in our clinic and the device that our patients use at home for self-measurement of their BP is the same most validated device in the world at a cost-effective price. This way we can be rest assured that our patients are well taken care of at home too, by this device. The maximum amplitude corresponds to the mean arterial pressure. There is a rising and falling phase, and the amplitude systolic is 55% of the maximum, while the amplitude diastolic is 70% of the maximum, in the case of normotensives with compliant arteries. But when the artery is stiff, then the maximum amplitude or mean arterial pressure is not steep enough for the algorithm to pick out the value of the mean arterial pressure (MAP) from the apex of the envelope. As the MAP or maximum amplitude algorithm is no longer the peak of the wave, but the wave itself

becomes a plateau. Hence the need to validate the device in such patients. In the case of stiff arteries, the corresponding values are not 50% and 70% but 45% and 90%, which one will know only if one validates the device. If we do not use validated devices, the BP reading could be fallacious. The algorithm is specifically designed to assess the envelopes in such populations and measure the blood pressure accordingly.

So it is not just an ISI mark which assures quality, reproducibility, and accuracy but a validation study done in every one of the 11 concomitant clinical conditions, as is the case with the Microlife device. From January 1, 2020 the DCGI will go through the BP measuring devices from a validation perspective before clearing the same for use in Indian patients. Ideally, doctors too should change over from their aneroid and mercury sphygmomanometers to the digital or automated oscillometric validated devices. The algorithm is proprietary and the property of the manufacturer of the device, a fiercely guarded secret.

But above and all, measurement of BP is a skill and an art. The patient should be asked to rest for about 5 minutes, empty the bladder, refrain from smoking, having tea/coffee, exercise, or alcohol for at least 30 min before measurement, the patient should be sitting comfortably upright with the back well supported, both feet firmly on the floor, legs not crossed, an appropriate cuff size should be used, no talking during the measurement, the arm should be at the level of the heart, deflation should be done at exactly 2-3 mm Hg decrements, the eye should be at level of the mercury column, BP measurement should be done in both arms and if the BP is higher in one of the two arms, that arm should be used for subsequent measurements, and in some cases,<sup>19</sup> e.g., diabetic and age-related dysautonomia, BP measurement should be done while standing, sitting and sleeping to rule out postural hypotension. The most important is whether the device is calibrated or validated and if yes, when this was done the last time.<sup>20</sup>

To conclude, it is high time we use automated or digital oscillometric validated algorithm based devices that are environmentally friendly. They are cost-effective as they can be used for all in the family. The doctors should insist that patients purchase such devices so that home BP measurements can be done, and the patient should bring their records to their doctor during follow up. Just like the diabetes patient has a glucometer at home, the asthma patient has a peak flow meter at home, a pyrexia patient has a thermometer at home, it is high time a validated BP meter also finds a place in the home of every patient. India is home to an estimated 234 million adults who have hypertension, per the CSI Prevent Great India BP survey. Per the Indian Guidelines on Hypertension-4, only 20% and 11% are controlled in urban and rural areas, respectively. But the moot questions are, is the diagnosis accurate (have we ruled out masked or white coat hypertension?), how is the BP being measured (an average of 3 readings is more accurate than just one reading), how often (once in a week/fortnight/month/3-6 months/year at least, depending on the patient), in which setting (clinic, home, ABPM), and by which device?.

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## Assessment of Target Organ Damage in Hypertensive Patients

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### ABSTRACT

Hypertension is a major cardiovascular risk factor. The aims of treating hypertension are more than just control of the blood pressure numbers and includes cardiovascular risk reduction. Hypertension mediated organ damage (HMOD) is a major concern in these patients as its presence increases the overall risk. Studies have shown that some of the HMOD like left ventricular hypertrophy (LVH) are markers of worse prognosis and regression of HMOD with treatment can improve prognosis. It is therefore very important that hypertensive patients are screened at regular intervals for signs of HMOD.

### INTRODUCTION

The European society of Hypertension defines Target organ damage (TOD) or Hypertension mediated organ damage (HMOD) as "Structural or functional changes in arteries or end organs (heart, blood vessels, brain, eyes, and kidney) caused by an elevated BP".<sup>1</sup> The common HMOD that are seen are left ventricular hypertrophy (LVH), Renal failure, hypertensive retinopathy, vascular changes and white matter changes or cognitive impairment. Involvement of the coronary and cerebral vasculature can lead to macrovascular complications such as ischemic heart disease and stroke.<sup>2</sup>

### PATHOPHYSIOLOGY

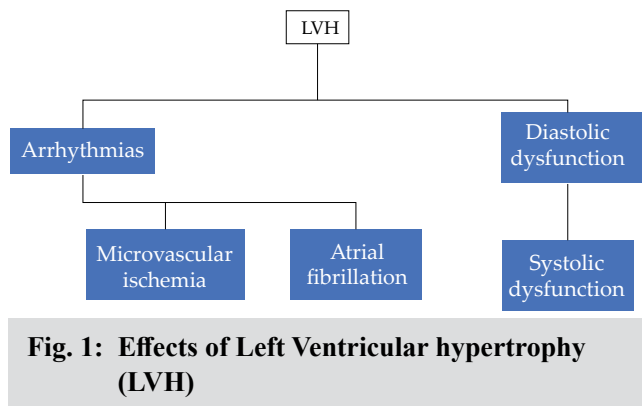
There are many pathophysiological mechanisms that lead to the development of these changes mentioned above. Hypertension

leads to platelet activation, endothelial dysfunction and impaired fibrinolysis and increased thrombogenesis. Each of these are inter-related and perpetuate the other. There is impaired angiogenesis and alterations in the matrix metalloproteinases. All these changes ultimately lead to collagen deposition and arteriolar thickening resulting in microvascular disease. The changes in the endothelium also lead to the formation of atheromatous plaques.<sup>2</sup>

### CLINICAL IMPORTANCE

The assessment of HMOD in newly diagnosed hypertensives is often neglected. It is however very important to assess these not only in newly diagnosed patients, but also during follow up of hypertensive patients. The presence of HMOD such as LVH in a newly diagnosed patient would indicate that the hypertension has been long standing, whereas the absence could indicate either white coat

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hypertension or recently developed hypertension. The presence of HMOD is indicative of increased overall cardiovascular risk of the patient. Some HMOD like LVH are independent predictors of poor prognosis in hypertensive patients.<sup>3</sup>

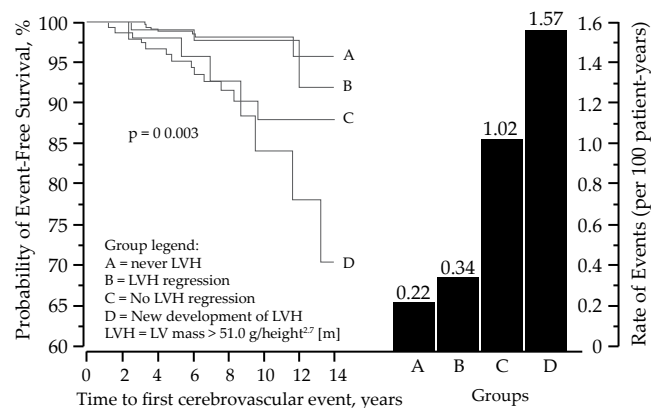
## LEFT VENTRICULAR HYPERTROPHY (LVH)

A pooled analysis of 30 studies involving >37,000 subjects by Cuspidi et al<sup>4</sup> found that the average incidence of LVH among hypertensive patients varies from around 36%-41%, although in some studies the incidence was as high as 77% of all hypertensives. It is more prevalent in patients of African heritage and there is no difference between the sexes. They also found that eccentric and Concentric hypertrophy were commonly seen though Eccentric geometry was slightly more prevalent.

ECG is often used as a screening method for LVH, however all the criteria that are commonly used such as the Sokolow-lyon or Cornells criteria, have a low sensitivity but high specificity.<sup>5</sup> Echocardiogram or Magnetic resonance imaging (MRI) are the gold standard for the diagnosis of LVH.

LVH can lead to many complications (Figure 1). It causes diastolic dysfunction which can lead to systolic dysfunction, It is also associated with arrhythmias including atrial fibrillation and it can cause microvascular ischemia leading to symptomatic angina.<sup>2</sup>

Many studies have repeatedly demonstrated that the presence of LVH is a poor prognostic



**Fig. 2: Risk of cerebrovascular events in relation to the previous changes in the echocardiographic features of left Ventricular Hypertrophy (LVH)<sup>6</sup>**

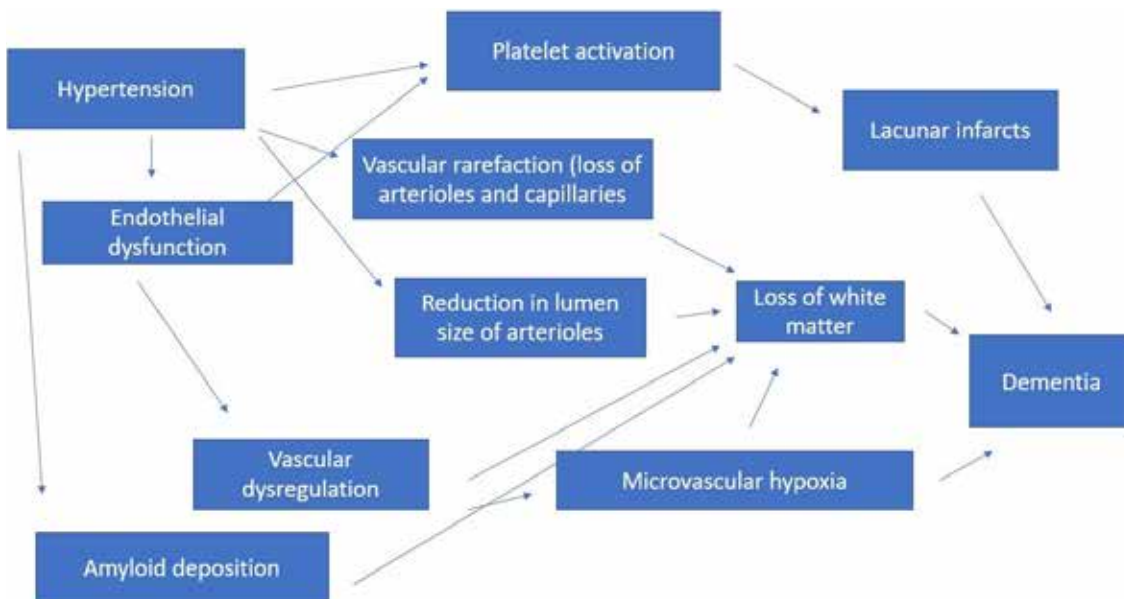
factor, whereby patients with LVH have an almost two fold increased risk of cardiovascular end points.<sup>3</sup> Similarly studies have shown that patients who have regression of LVH on treatment have the best prognosis, (almost similar to those without LVH) as compared to those where the LVH does not regress or indeed where there is development of new LVH<sup>6</sup> (Figure 2).

The guidelines recommend performing a 12 lead ECG in all patients with hypertension. They however, recommend performing a transthoracic echocardiogram to rule out LVH only where there is a clinical or electrocardiographic evidence or suspicion of LVH.<sup>1</sup>

## CEREBROVASCULAR DISEASE

Hypertension is a risk factor for strokes and cognitive impairment. Hypertension is present in upto 84% of patients with stroke<sup>7</sup> and almost 30% of patients who develop a stroke or TIA have significant cognitive decline at 30 days.<sup>8</sup> Even in patients who do not have a stroke, the risk of cognitive impairment and full blown dementia is much higher in hypertensive than non- hypertensive patients.<sup>9</sup>

The mechanisms of cognitive impairment are similar as those causing the other HMOD. There is endothelial dysfunction and platelet activation which leads to vascular dysregulation, vascular rarefaction of the arterioles and capillaries, microthrombi, lacunar



**Fig. 3: Pathogenesis of Dementia and cognitive impairment in Hypertension**

infarcts which leads to loss of white matter and ultimately cognitive impairment<sup>10</sup> (Figure 3).

It has been shown in the Syst-Eur study that treatment of hypertension especially in the elderly can cause a significant reduction in the incidence of new dementia.<sup>11</sup> The PROGRESS-MRI study also showed that strict blood pressure control with perindopril stopped or slowed down the white matter loss on MRI.<sup>12</sup> The SPRINT MIND study also showed a significant reduction in the incidence of cognitive decline and new dementia with strict blood pressure control.<sup>13</sup> However, other studies have shown that in the elderly population, lowering blood pressure to below 120 mmHg, can also lead to worsening cognitive functions.<sup>14</sup> Therefore, we have to aim for blood pressures that are not below 120 mmHg systolic. The ESH guidelines recommend brain MRI or CT only in hypertensive patients with neurological symptoms and/or cognitive impairment to rule out brain infarctions, microbleeds and white matter lesions.<sup>1</sup>

## RENAL FAILURE

Hypertension is a leading cause of renal dysfunction.<sup>15</sup> It is interesting because renal

failure due to other causes can lead to hypertension. Therefore, it becomes a vicious cycle when a hypertensive patient develops renal failure. The main mechanisms involved here are arteriosclerosis, endothelial dysfunction, microinfarcts, disruption of renal autoregulation, barotrauma and ultimately glomerular necrosis and damage and loss of nephrons. The changes are initially benign nephrosclerosis which over time leads to malignant nephrosclerosis.<sup>15</sup> The ESH guidelines recommend that all hypertensive patients should have the serum creatinine and glomerular filtration rate (eGFR) measured, along with the urine albumin creatinine ratio. Renal ultrasound and doppler should be considered in patients with impaired renal function, albuminuria or for suspected cases of secondary hypertension.<sup>1</sup>

## VASCULAR DISEASE

Hypertension damages the micro and microvasculature. There are many tests that can be done to assess vascular function.<sup>16</sup> Flow mediated dilatation measures the integrity of the endothelium whilst the carotid intima media thickness measures the level of atheroma burden in the microvasculature. The pulsatility index or pulse wave velocity assesses the stiffness of the arteries and is

performed in the carotid or femoral arteries. A value of >10 m/s is considered abnormal. The ankle brachial index value of <0.9 indicated significant lower limb arterial disease. The ESH guidelines recommend performing these tests only if peripheral vascular disease is suspected.<sup>1</sup>

## HYPERTENSIVE RETINOPATHY

The prevalence of hypertensive retinopathy varies from around 30% to 70% depending on the study quoted.<sup>17</sup> The mechanisms involved here are similar to the other HMOD with endothelial dysfunction, platelet activation, arteriosclerosis and vascular dysregulation. The presence of hypertensive retinopathy has been shown to correlate with other HMOD such as renal dysfunction, cognitive impairment, LVH and vascular disease.<sup>18</sup>

The ESH guidelines recommend routine fundoscopy in patients with grade 2 or 3 hypertension with diabetes as a class I indication and as a class IIb indication in all other hypertensives.<sup>1</sup>

## SURVEILLANCE OF HMOD

The ESH or the AHA guidelines do not have any recommendations regarding regular monitoring of patients with hypertension for their HMOD. However, regular surveillance is useful as it has been shown to have prognostic value. As described earlier regression of LVH is associated with improved prognosis. It would be beneficial to have specialised hypertension clinics similar to those for diabetes, where hypertensive patients can be screened annually for the presence of HMOD.<sup>19</sup> It is hoped that these clinics will help improve the care of our hypertensive patients and will help with surveillance of HMOD

## CONCLUSION

Hypertension is an important risk factor for cardiovascular disease. It affects many organ systems. All newly diagnosed hypertensive patients should be screened for HMOD and regular follow up is helpful. Proper control of blood pressure and risk management is

important for improved prognosis in hypertensive patients.

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## Diuretics – In Hypertension

Rajesh Kumar Jha<sup>1</sup>

### ABSTRACT

Antihypertensive monopharmacotherapy with diuretics renders blood pressure (BP) values under control in a large percentage of patients suffering from essential hypertension, and it reduces cardiovascular morbidity and mortality. Effective once-daily treatment with a diuretic controls high BP over 24 h. Diuretics are effective in adult and elderly hypertensive subjects. Diuretics are the second most commonly prescribed class of antihypertensive medication, and thiazide-related diuretics have increased at a rate greater than that of other antihypertensive medications. The latest hypertension guidelines have underscored the importance of diuretics for all patients. This review focuses on the use of diuretics as the long-term therapy for hypertension; pathophysiology, classification of antihypertensives and newer guidelines are briefly considered.

### INTRODUCTION & EPIDEMIOLOGY

Hypertension is a common lifestyle disorder and is a very strong risk factor for cardiovascular diseases (CVDs).

It is estimated that it increases the risk at least two fold for CVDs including coronary artery disease (CAD), congestive heart failure (CHF), stroke, renal failure and peripheral artery disease.

Hypertension is a global disease, but its prevalence varies amongst countries and sub – populations.

The prevalence of hypertension increases with growing age and it is estimated that starting from around 15 - 20% in the early age while it

increases to 75 – 80% in individuals above 70 years of age.

In India due to varied distribution of the population exact prevalence of hypertension cannot be estimated. However, several regional small scale surveys with varying protocols have reported a prevalence of 6.1 - 36.3% in men and 2 – 39.4% in women in urban areas and 3 – 36% in men and 5.8 – 37.2% in women in rural areas, respectively.

### PREDISPOSING FACTOR

A strong familial and genetic pre – disposition exists, and a number of modifiable risks factors have been identified.

- Genetic → Epidemiological studies suggest that 20 – 60% of essential hypertension is inherited while the remainder is acquired / environmental.

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**Table 1: JNC 8**

Classification	Systolic BP (mm Hg)	And	Diastolic BP (mm Hg)
Normal	<120	And	<80
Prehypertension	120-139	Or	80-89
Stage 1 hypertension	140-159	Or	90-99
Stage 2 hypertension	≥160	Or	≥100

- Age & Sex → Almost all surveys demonstrated that BP increases with age in both the genders.

However, in adult women BP is lower than in men of comparable age but it increases thereafter being equivalent in middle – age; higher in later life in females.

- Salt intake → An Intersalt study (n= 10, 079) inclusive of both genders from 32 countries demonstrated that consumption of 100mg of salt per day declines BP by 9mm hgin the age group 25 – 55 years.
- Alcohol intake → Consumption of excessive alcohol is another important risk factor for development of hypertension.
- It accounts for 5 – 30 % of all hypertension.
- Smoking → Tobacco smoking has been reported to be an important precursor for development of hypertension.
- Physical activity → Sedentary individuals have 20 -50 % increased risk of developing hypertension.

## CLASSIFICATION OF HYPERTENSION

In 2014, The Eighth Joint National Committee released evidence-based guidelines for the management of high blood pressure in adults, including treatment thresholds, target BP goals, and specific medications (Table 1).

A major change in JNC-8 was the shift to more permissive (higher) blood pressure goals.

In 2017, the American Heart Association and the American College of Cardiology (Table 2) released another set of hypertension guideline that proposed new hypertension definitions and advised stricter blood pressure control.

These guidelines focused on stricter treatment thresholds, lower target BP goals, called for more accurate blood pressure monitoring,

**Table 2: ACC/AHA 2017**

BP Category	Systolic BP (mm Hg)	And	Diastolic BP (mm Hg)
Normal	<120	And	<80
Elevated	120-129	And	<80
Hypertension			
Stage 1 hypertension	130-139	Or	80-89
Stage 2 hypertension	≥140	Or	≥90

and highlighted the need for lifestyle changes.

## PATHOPHYSIOLOGY

Sodium and fluid balance and vasomotor tone are cornerstones in blood pressure regulation. Both mechanisms are affected by numerous genetic and environmental factors, and are controlled by hormonal, nervous system, paracrine, and intracellular feedback loops. The interactions between these factors (Figure 1) change with age, and account for the heterogeneous pattern of the haemodynamic alterations that lead to and sustain high blood pressure throughout life.

## JNC 8

- Patients < 60 years of age: start pharmacotherapy at 140/90 mmHg.
- Patients with diabetes: start pharmacotherapy at 140/90 mmHg.
- Patients with CKD: start pharmacotherapy at 140/90 mmHg.
- Patients 60 years of age and older: start pharmacotherapy at 150/90 mmHg

## BLOOD PRESSURE GOAL

- Patients <60 years of age- <140/90 mmHg
- Patients with diabetes- <140/90 mmHg
- Patients with CKD: <140/90 mmHg
- Patients 60 years of age and older: <150/90 mmHg

## ACC/AHA 2017<sup>1</sup>

### General

- Clinical CVD or 10-year ASCVD risk ≥ 10% - start pharmacotherapy at ≥130/80

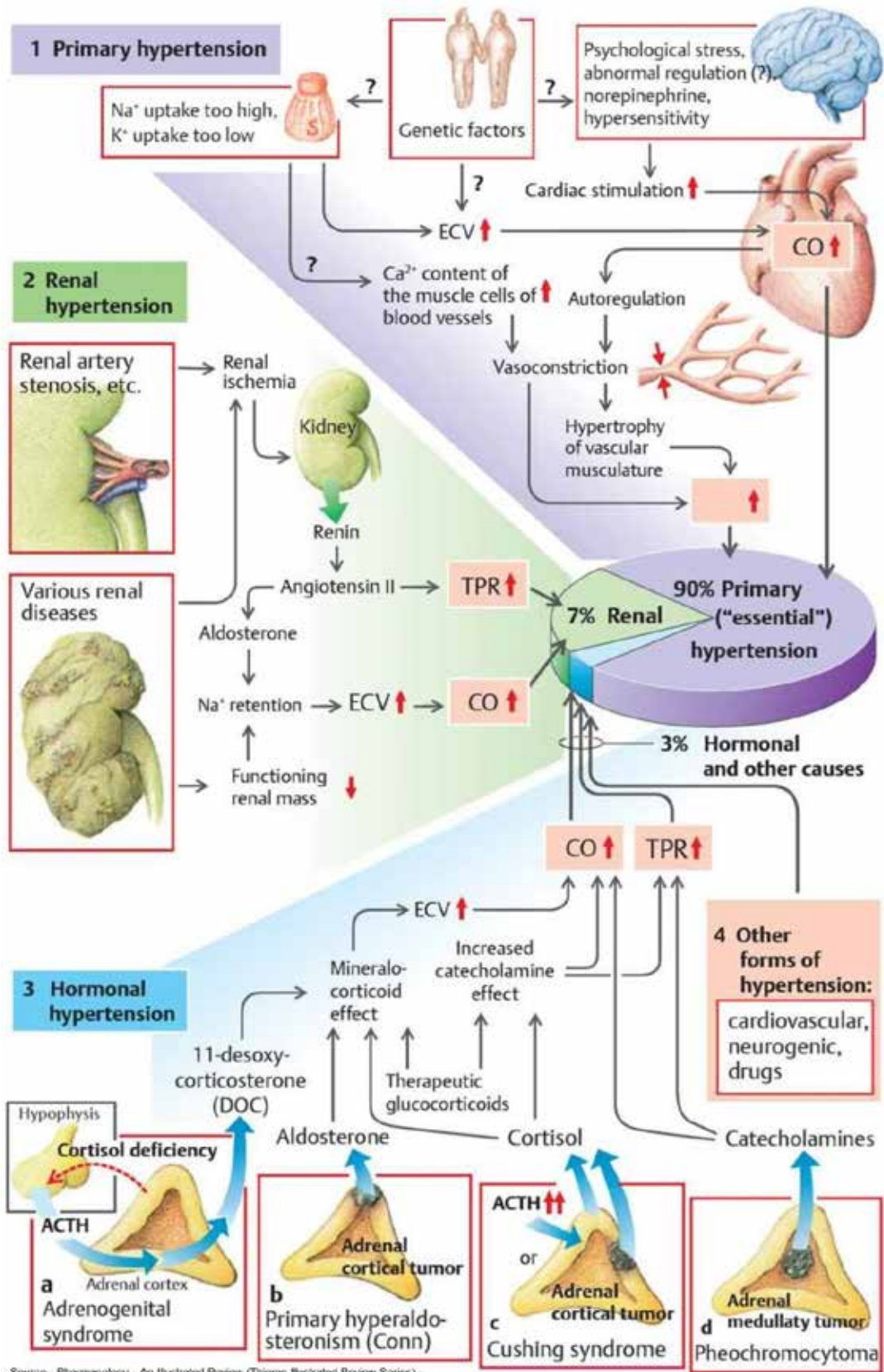


Fig. 1: Pathophysiology (from Pharmacology - An Illustrated Review), Treatment, Guidelines for treatment of Hypertension – JNC 8 Vs ACC/AHA 2017

**Table 3: Classification of Antihypertensives**

Class	Drug	Usual Dose, Range (mg per day)*	Daily Frequency	Comments
<i>Primary Agents</i>				
Thiazide or thiazide-type diuretics	<b>Chlorthalidone</b>	12.5-25	1	<ul style="list-style-type: none"> <li>Chlorthalidone preferred based on prolonged half-life and proven trial reduction of CVD</li> <li>Monitor for hyponatremia and hypokalemia, uric acid and calcium levels.</li> <li>Use with caution in patients with history of acute gout unless patient is on uric acid-lowering therapy.</li> </ul>
	<b>Hydrochlorothiazide</b>	25-50	1	
	<b>Indapamide</b>	1.25-2.5	1	
	<b>Metolazone</b>	2.5-5	1	
ACE Inhibitors	<b>Benazepril</b>	10-40	1 or 2	<ul style="list-style-type: none"> <li>Do not use in combination with ARBs or direct renin inhibitor</li> <li>Increased risk of hyperkalemia, especially in patients with CKD or in those on K+ supplements or K+-sparing drugs</li> <li>May cause acute renal failure in patients with severe bilateral renal artery stenosis</li> <li>Do not use if history of angioedema with ACE inhibitors.</li> <li>Avoid in pregnancy</li> </ul>
	<b>Captopril</b>	12.5-150	2 or 3	
	<b>Enalapril</b>	5-40	1 or 2	
	<b>Fosinopril</b>	10-40	1	
	<b>Lisinopril</b>	10-40	1	
	<b>Moexipril</b>	7.5-30	1 or 2	
	<b>Perindopril</b>	4-16	1	
	<b>Quinapril</b>	10-80	1 or 2	
	<b>Ramipril</b>	2.5-20	1 or 2	
<b>Trandolapril</b>	1-4	1		
ARBs	<b>Azilsartan</b>	40-80	1	<ul style="list-style-type: none"> <li>Do not use in combination with ACE inhibitors or direct renin inhibitor</li> <li>Increased risk of hyperkalemia in CKD or in those on K+ supplements or K+-sparing drugs</li> <li>May cause acute renal failure in patients with severe bilateral renal artery stenosis</li> <li>Do not use if history of angioedema with ARBs. Patients with a history of angioedema with an ACEI can receive an ARB beginning 6 weeks after ACEI discontinued.</li> <li>Avoid in pregnancy</li> </ul>
	<b>Candesartan</b>	8-32	1	
	<b>Eprosartan</b>	600-800	1 or 2	
	<b>Irbesartan</b>	150-300	1	
	<b>Losartan</b>	50-100	1 or 2	
	<b>Olmesartan</b>	20-40	1	
	<b>Telmisartan</b>	20-80	1	
	<b>Valsartan</b>	80-320	1	
CCB-dihydropyridines	<b>Amlodipine</b>	2.5-10	1	<ul style="list-style-type: none"> <li>Avoid use in patients with HFrEF; amlodipine or felodipine may be used if required</li> <li>Associated with dose-related pedal edema, which is more common in women than men</li> </ul>
	<b>Felodipine</b>	2.5-10	1	
	<b>Isradipine</b>	5-10	2	
	<b>Nicardipine SR</b>	60-120	2	
	<b>Nifedipine LA</b>	30-90	1	
	<b>Nisoldipine</b>	17-34	1	
CCB-nondihydropyridines	<b>Diltiazem ER</b>	120-360	1	<ul style="list-style-type: none"> <li>Avoid routine use with beta blockers due to increased risk of bradycardia and heart block</li> <li>Do not use in patients with HFrEF</li> <li>Drug interactions with diltiazem and verapamil (CYP3A4 major substrate and moderate inhibitor)</li> </ul>
	<b>Verapamil IR</b>	120-360	3	
	<b>Verapamil SR</b>	120-360	1 or 2	
	<b>Verapamil-delayed onset ER</b>	100-300	1 (in the evening)	

Table is continued in the next two pages

Class	Drug	Usual Dose, Range (mg per day)*	Daily Frequency	Comments
<i>Secondary Agents</i>				
Diuretics-loop	<b>Bumetanide</b>	0.5-2	2	<ul style="list-style-type: none"> <li>Preferred diuretics in patients with symptomatic HE Preferred over thiazides in patients with moderate-to-severe CKD (e.g., GFR &lt;30 ml/min)</li> </ul>
	<b>Furosemide</b>	20-80	2	
	<b>Torsemide</b>	5-10	1	
Diuretics—potassium sparing	<b>Amiloride</b>	5-10	1 or 2	<ul style="list-style-type: none"> <li>Monotherapy agents minimally effective antihypertensives</li> <li>Combination therapy of potassium sparing diuretic with a thiazide can be considered in patients with hypokalemia on thiazide monotherapy</li> <li>Avoid in patients with significant CKD (e.g., GFR &lt;45 ml/min)</li> </ul>
	<b>Triamterene</b>	50-100	1 or 2	
Diuretics—aldosterone antagonists	<b>Eplerenone</b>	50-100	1 or 2	<ul style="list-style-type: none"> <li>Preferred agents in primary aldosteronism and resistant hypertension</li> <li>Spironolactone associated with greater risk of gynecomastia and impotence compared to eplerenone</li> <li>Common add-on therapy in resistant hypertension</li> <li>Avoid use with K+ supplements, other K+-sparing diuretics or significant renal dysfunction</li> <li>Eplerenone often requires twice daily dosing for adequate BP lowering</li> </ul>
	<b>Spironolactone</b>	25-100	2	
Beta blockers-cardioselective	<b>Atenolol</b>	25-100	2	<ul style="list-style-type: none"> <li>Beta blockers are not recommended as first-line agents unless the patient has IHD or HF</li> <li>Preferred in patients with bronchospastic airway disease requiring a beta blocker</li> <li>Bisoprolol and metoprolol succinate preferred in patients with HFrEF</li> <li>Avoid abrupt cessation</li> </ul>
	<b>Betaxolol</b>	5-20	1	
	<b>Bisoprolol</b>	2.5-10	1	
	<b>Metoprolol tartrate</b>	100-200	2	
	<b>Metoprolol succinate</b>	50-200	1	
Beta blockers-cardioselective and vasodilatory	<b>Nebivolol</b>	5-40	1	<ul style="list-style-type: none"> <li>Induces nitric oxide-induced vasodilation</li> <li>Avoid abrupt cessation</li> </ul>
Beta blockers-noncardioselective	<b>Nadolol</b>	40-120	1	<ul style="list-style-type: none"> <li>Avoid in patients with reactive airways disease</li> <li>Avoid abrupt cessation</li> </ul>
	<b>Propranolol IR</b>	80-160	2	
	<b>Propranolol LA</b>	80-160	1	
Beta blockers-intrinsic sympathomimetic activity	<b>Acebutolol</b>	200-800	2	<ul style="list-style-type: none"> <li>Generally avoid, especially in patients with IHD or HF</li> <li>Avoid abrupt cessation</li> </ul>
	<b>Penbutolol</b>	10-40	1	
	<b>Pindolol</b>	10-60	2	
Beta blockers-combined alpha- and beta-receptor	<b>Carvedilol</b>	12.5-50	2	<ul style="list-style-type: none"> <li>Carvedilol preferred in patients with HFrEF</li> <li>Avoid abrupt cessation</li> </ul>
	<b>Carvedilol phosphate</b>	20-80	1	
	<b>Labetalol</b>	200-800	2	

Table is continued in the next page

Class	Drug	Usual Dose, Range (mg per day)*	Daily Frequency	Comments
<i>Secondary Agents (continued from previous page)</i>				
Direct renin inhibitor	<b>Aliskiren</b>	150-300	1	<ul style="list-style-type: none"> <li>Do not use in combination with ACE inhibitors or ARBs</li> <li>Aliskiren is very long acting</li> <li>Increased risk of hyperkalemia in CKD or in those on K+ supplements or K+ sparing drugs</li> <li>May cause acute renal failure in patients with severe bilateral renal artery stenosis</li> <li>Avoid in pregnancy</li> </ul>
Alpha-1 blockers	<b>Doxazosin</b>	1-16	1	<ul style="list-style-type: none"> <li>Associated with orthostatic hypotension, especially in older adults</li> <li>May consider as second-line agent in patients with concomitant BPH</li> </ul>
	<b>Prazosin</b>	2-20	2 or 3	
	<b>Terazosin</b>	1-20	1 or 2	
Central Alpha2-agonists and other centrally acting drugs	<b>Clonidine oral</b>	0.1-0.8	2	<ul style="list-style-type: none"> <li>Generally reserved as last-line due to significant CNS adverse effects, especially in older adults</li> <li>Avoid abrupt discontinuation of clonidine, which may induce hypertensive crisis; clonidine must be tapered to avoid rebound hypertension</li> </ul>
	<b>Clonidine patch</b>	0.1-0.3	1 weekly	
	<b>Methyldopa</b>	250-1000	2	
	<b>Guanfacine</b>	0.5-2	1	
Direct vasodilators	<b>Hydralazine</b>	100-200	2 or 3	<ul style="list-style-type: none"> <li>Associated with sodium and water retention and reflex tachycardia; use with a diuretic and bet a blocker</li> <li>Hydralazine associated with drug-induced lupuslike syndrome at higher doses</li> <li>Minoxidil associated with hirsutism and requires a loop diuretic. Can induce pericardial effusion</li> </ul>
	<b>Minoxidil</b>	5-100	1 -3	

- No clinical CVD and 10-year ASCVD risk < 10%- start pharmacotherapy at  $\geq 130/80$
- Older persons ( $\geq 65$  years of age; non-institutionalized, ambulatory, community-living adults)- start pharmacotherapy at  $\geq 130/80$

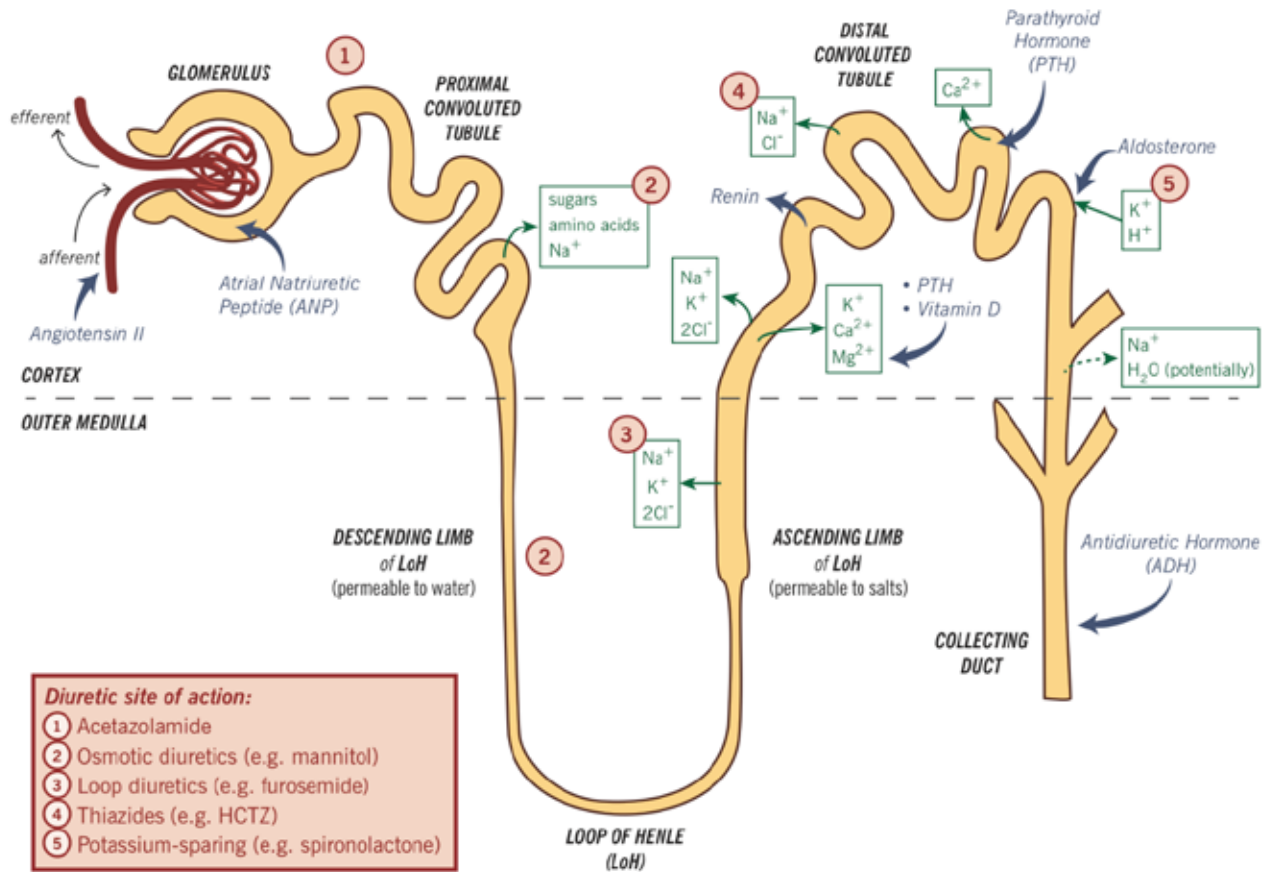
### Specific Comorbidities

- Diabetes mellitus - start pharmacotherapy at  $\geq 130/80$
- Chronic kidney disease - start pharmacotherapy at  $\geq 130/80$
- Chronic kidney disease post-renal transplantation - start pharmacotherapy at  $\geq 130/80$

- Heart failure - start pharmacotherapy at  $\geq 130/80$
- Stable ischemic heart disease - start pharmacotherapy at  $\geq 130/80$
- Secondary stroke prevention - start pharmacotherapy at  $\geq 140/90$
- Peripheral arterial disease- start pharmacotherapy at  $\geq 140/90$

### Blood pressure goal

- Clinical CVD or 10-year ASCVD risk  $\geq 10\%$  -  $< 130/80$
- No clinical CVD and 10-year ASCVD risk  $< 10\%$ -  $< 130/80$
- Older persons ( $\geq 65$  years of age; non-insti-



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Fig. 2: Site of action of Diuretics(from McMaster Pathophysiology review)

tutionalized, ambulatory, community-living adults)- <130(SBP)

### Specific Comorbidities

- Diabetes mellitus - <130/80
- Chronic kidney disease - <130/80
- Chronic kidney disease post-renal transplantation - <130/80
- Heart failure - <130/80
- Stable ischemic heart disease - <130/80
- Secondary stroke prevention - <130/80
- Peripheral arterial disease- <130/80

### ROLE OF DIURETICS

Diuretics is used as one of the first-line treatments for patients with essential hyper-

tension (Table 3). This choice is based on the observation that a wide range of patients can benefit from diuretics, which counter the extracellular volume expansion and the salt retention associated with hypertension and reduce morbidity and mortality. For most patients, the risk of a clinically meaningful change in laboratory parameters is rather low, whereas the clinical benefits of diuretics are high.

Their proposed site of action is shown in Figure 2.

The American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines, for instance, name the reduction of clinical events as the main criterion for endorsing any antihypertensive medication and cite results of meta-analyses

that show that diuretics perform as well as angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers<sup>1</sup> (CCB), and angiotensin receptor blockers. These meta-analyses include key randomized controlled trials, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT; N=33357), which is of interest because it compared the long-term effects of treatment with chlorthalidone, amlodipine and lisinopril.<sup>2</sup> In this cohort of hypertensive patients who had at least one other coronary heart disease risk factor, no significant between-group differences were found for the primary outcome (combined fatal coronary heart disease or nonfatal myocardial infarction) or for all-cause mortality. Higher fasting glucose levels were observed with chlorthalidone, but there was no conclusive evidence that the modestly increased risk of developing diabetes mellitus resulted in an increased risk of other clinical events.<sup>3</sup>

## CONCLUSION

Hypertension is a common lifestyle disorder and is a very strong risk factor for cardiovascular diseases (CVDs).

Despite of varied lifestyle modifications and non - pharmacological measures the prevalence of hypertension is increasing due to several risk factors.

In pharmacological therapies there are numerous sub - groups of anti - hypertensives which exerts their effect via different mechanisms.

The choice of anti - hypertensive depends upon the patient's age group, laboratory parameters, drug interactions, cost efficacy,

absolute / relative contra - indications and various other factors.

Medium efficacy diuretics (Thiazides / Thiazide - like) have been proven as a one of the primary agents in the management of hypertension.

Chlorthalidone, is found to be superior than ACE / long acting CCB's in the prevention of CVD's. ALLHAT meta-analysis showed that thiazides reduce incidence of HFrEF as compared to CCB's.

Numerous studies & evidence has reported the potency & efficacy of diuretics in the management of hypertension with subsequent reduction in the CV risk.

Hence, diuretics especially medium efficacy should be promoted as primary drug in hypertension.

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# Clinical Profile of Isolated Systolic Hypertension in Elderly Patients in Tertiary Care Hospital

Thahir Baig M

## ABSTRACT

**Introduction:** Isolated Systolic Hypertension (ISH) defined as systolic blood pressure  $\geq 140$  mmHg and diastolic blood pressure  $< 90$  mmHg. The prevalence of Isolated Systolic Hypertension is higher in elderly age and is a major risk factor for cardiovascular morbidity and mortality.

**Material:** This is a cross sectional study with a sample size of 60 patients with Isolated systolic hypertension of age above 60 years. Data like history, age, sex, height, weight, body surface area, waist-hip ratio, blood pressure recording, systemic examination, Fasting and post-prandial blood sugars, Blood urea, Serum creatinine, Lipid profile, electrocardiography, echocardiogram were done and results analysed.

**Observations:** The study population included 39 males and 21 females with a mean age of  $70.88 \pm 6.13$  years. 23 (38.33%) Patients with Stage 1 ISH (140-159) are 23 (38.33%) and 37 (61.67%) patients were in the Stage 2 ( $\geq 160$ ). 35 (58.33%) were asymptomatic. 17 (28.33%) patients have BMI more than 25.0. 31 (51.67%) patients have raised waist/hp ratio, 24 (40.0%) patients were diabetic, and 23 (38.33%) patients have Dyslipidemia. 43 patients showed retinal changes. 21 (35.0%) patients had ECG- LVH as per Sokolow-Lyons criteria. 14 (23.3%) patients showed reduced ejection fraction in echocardiogram.

**Conclusions:** Screening of ISH and co-morbidities should be done in all elderly patients to reduce morbidity and mortality.

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# Recurrent Hypoglycemia in Non-diabetic Patient with ACE Inhibitor – A Case Report

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Mohammed Riyaz, Imran AS, Mohammed Muzammil

## ABSTRACT

**Introduction:** Recurrent severe hypoglycemia in a non-diabetic patient caused by lisinopril.

**Observations:** This is a 60 yr old non diabetic female with past medical h/o hypertension presented to ER with abrupt onset of confusion and found to have blood glucose of 25 mg/dL that responded to IV Dextrose with complete resolution of her symptoms. However hypoglycemia recurred, requiring dextrose drip. H/o OAD drug intake – none, Ultrasound and CT Abdomen normal. TFT, HbA1C CBP, RFT, Insulin, C-peptide were normal. Cosyntropin test normal. Patient again readmitted with hypoglycemia. 72-hour fasting test showed non-insulin mediated hypoglycemia (RBS:51 mg/dL: Insulin level 25mU/L, c-peptide 1.1ng/ml. multiple admission with recurrent hypoglycemia over 1 month, and reviewing the other causes of hypoglycemia, it was noted that the episodes of hypoglycemia occurred after increasing the dose of lisinopril from 10 mg to 20 mg for her uncontrolled HTN. We had stopped lisinopril and monitored the patient since then no hypoglycemia has occurred. ACE inhibitors induced hypoglycemia reported in 1985. It is hypothesized, that it indirectly increase sensitivity of insulin by increasing the circulating kinine which in eventually leads to vasodilatation in muscle and increase glucose uptake.

**Conclusions:** Hypoglycemia is a very rare side effect of ACE inhibitors in diabetic patients. Physician should be aware.

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Esani Diabetes and Multispeciality Centre

# To Evaluate the Status of Hypertension Control, Status of Associated Co-Morbidity and Cardiovascular Risk Factors in Hypertensive Population

Annukumar Sahani, RP Ram

## ABSTRACT

**Introduction:** Hypertension is an important global health burden and challenge because of its high prevalence and resulting cardiovascular disease and chronic kidney disease. Uncontrolled hypertension (which is defined as inability to achieve the SBP 130 mm Hg and DBP 80 mm Hg as per SPRINT TRAIL and ESC/ESH 2018 guidelines, despite being on anti-hypertensive medications) is associated with increased mortality.

**Material:** This was a cross sectional,observational study where 170 patients presenting with hypertension in the OPD were assessed via a pre-designed, protocol to obtain status of Bp control, number of pills consumption, associated co-morbidity, risk factors and impact of lifestyle. Statistical analysis was done using SPSS version 20.

**Observations:** Out of 170 patient 99 (58.2%) had controlled hypertension while 71 (41.8%) had uncontrolled hypertension. Obesity, Excessive alcohol intake, tobacco consumption, sedentary lifestyle were found to be significantly associated with uncontrolled hypertension.

**Conclusions:** Awareness of the hypertension status with focus being on improving health literacy to decrease the dangers of uncontrolled hypertension is the need of the hour. Interventions like weight management, increased physical activity, and reduction in tobacco and alcohol use are required and recommended.

Jaslok Hospital And Research Centre

# A Study of 24 hours Ambulatory Blood Pressure Among Resident Doctors Working at a Tertiary Care Hospital in Northern India

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**Shubhanshu Shivhare, Kamal Kumar Sawlani, Virendra Atam, Kauser Usman, Shyam Chand Chaudhary, D Himanshu**

## **ABSTRACT**

**Introduction:** Hypertension is one of the important modifiable risk factor for various cardiovascular diseases. Currently ambulatory blood pressure monitoring (ABPM) has incorporated in diagnosis of hypertension in various practice guidelines. It helps not only in identification of white coat, masked & nocturnal hypertension but it can also be used to see effect of stress on hypertension by a dipping pattern in different working environment.

**Material:** 159 junior residents working at various clinical & non-clinical departments of King George Medical University Lucknow, a tertiary care hospital in northern India, during a period of one year were enrolled in this observational study. Each resident underwent Clinic BP measurement followed by ABPM for a 24hour period and comparison was done between these two groups.

**Observations:** The prevalence of white coat and masked hypertension is seems to be higher in both group while non-dipping pattern is higher in clinical group compared to non-clinical group.

**Conclusions:** This study shows that white coat and masked hypertension both are more prevalent among residents. More working hours, less sleeping hours and more stressful conditions at clinical departments could be the important factors for the higher non-dipping pattern and this can lead to worse cardiovascular outcomes in the future.

# A Study of Serum Uric Acid Level in Essential Hypertension

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**Rajeev Bhardwaj, Rajesh Jain**

## **ABSTRACT**

**Introduction:** Hypertension is leading killer disease in the world there is strong correlation between BP and risk of cardiovascular disease serum uric acid was first noted to be associated with increased bp by fredrick. Aim of this study is to find the association of serum uric acid levels with hypertension.

**Material:** This case control study was conducted in JLN hospital ajmer for 12 months from august 2017 to july 2018 A total of 200 patients were studied of which 100 essential hypertensive patients were cases and 100 were controls who were without hypertension. Patients with renal failure chronic inflammatory diseases such as rheumatod arthritis gout and sarcoidosis and patients with secondary hypertension were not included in the study.

**Observations:** It was observed that the value of mean serum uric acid was 5.6 mg% significantly more in cases than control group 4.3 mg% Values rises with severity of hypertension.

**Conclusions:** There is definite association between uric acid levels and hypertension serum uric acid levels have direct relation to the severity and duration of hypertension serum uric acid can be used as biochemical marker to determine the severity and duration of hypertension.

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JLN Medical College, Ajmer

# Study of Obstructive Sleep Apnoea in Patients with Hypertension

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**Archana Rao**

## **ABSTRACT**

**Introduction:** OSA is a chronic condition characterized by repetitive, partial or complete collapse of upper airways during sleep, associated with increasing respiratory efforts, intermittent arterial oxygen desaturation, systemic and pulmonary arterial blood pressure surges and sleep disruption. OSA is an important secondary causes and an independent risk factor for hypertension.

**Material:** A total of 76 patients with systemic hypertension attending OPD from August 2018 to 2019 were included for the study. Clinical and demographic data was collected. Hypertensive patients with an ESS score of over 10 underwent limited polysomnography. Patients were diagnosed as with and without OSA and their characteristics were compared.

**Observations:** Among 76 hypertensive patients, mean age group was 59 years, 48.7% were males, 51.3% were females and 63.8% had OSA. BMI, neck circumference, waist circumference, SBP, Obesity, Resistant HTN showed statistically significant association in OSA group as compared to Non OSA group ( $p < 0.05$ ).

**Conclusions:** The present results could contribute to an increased identification of OSA among patients with hypertension. We have found that among hypertensive patients, the presence of OSA was associated with greater frequency of co-morbidities and risk factors. Thus, the need for screening hypertensive patients for OSA has been reinforced by this study, especially if HTN is refractory.

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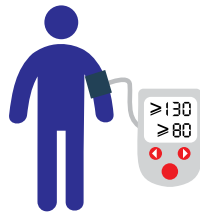
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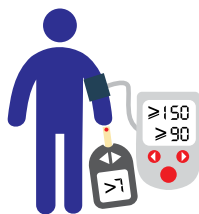
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