

## “A Cross Sectional, Observational Study of the Antihypertensive Pharmacotherapeutic Profile in an Urban Indian Adult Population”

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### Abstract

**Aims And Objectives:** As of 2016, An estimated 180 million people in India have primary hypertension. We set out to investigate the pharmacotherapeutic profile in this vast and varied population. Our objective was to assess what fraction of our study population was on medication in accordance to the best available contemporary medical evidence by comparing our results with 05 International guidelines published in the past 06 years.

**Methods:** We studied 1081 patients with a previous diagnosis of primary hypertension and analyzed the anti-hypertensives they were on, which had been prescribed from various urban and rural centers. Some of these patients were on our follow up as outpatients, while others were migrating from other medical setups. It was our endeavor to study a sample size large enough so that extrapolation to the general population was not an obstacle.

**Results:** Of the 1081 patients studied, 38.4% (35.5 – 41.3 with 95% CI) were on calcium channel blockers alone, 30.0 % (27.2 – 32.7 with 95% CI) were on a combination of calcium channel blockers and beta blockers, 14.1 % (12.09 – 16.25 with 95% CI) were on diuretics alone, 15.09% (12.96 – 17.23 with 95% CI) and 2.31 % (1.42 – 3.21 with 95% CI) were on other medication which includes beta blockers alone, alpha blockers alone and vasodilators.

**Conclusion:** The study shows that while most of the study population was on medication according to the latest guidelines, there was a considerable portion 30.0 % (27.2 – 32.7 with 95% CI) of the patient population was on beta blockers without adequate indications. (This is, however, still in accordance with the CHEP and ESH guidelines). The availability of safer and better options makes this a cause of concern. Considering the rampant prevalence of essential hypertension in Indian subcontinent, the authors feel that this study was not powered to be able to draw a conclusion for the entire demographic. A larger study in this regard is required.

**Keywords:** hypertension, JNC 8, angiotensin converting enzyme inhibitors, angiotensin receptor blockers

**Abbreviations:** JNC – Joint national committee, ARB – angiotensin receptor blockers, CCB – calcium channel blockers

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### I. Introduction

Hypertension is one of major constituents of the global disease burden. 15% of all deaths and an additional 92 million disability adjusted life years were attributable to hypertension<sup>1</sup>. It doubles the risk of cardiovascular disease, ischemic heart disease, renal failure and peripheral arterial disease. Estimates suggest that one in three adults have this condition, which has been defined as a systolic blood pressure of >140 mmHg and a diastolic pressure of >90 mmHg or taking anti-hypertensive medication<sup>2</sup>. Obesity and weight gain are independent risk factors for hypertension.

Twin and adoption studies show that there is a heritable component to the development of hypertension. High blood pressure before that age of 58 occurs 3.8 times more frequently among persons with a positive family history of hypertension<sup>1</sup>. Genes that encode parts of renin angiotensin system along with ACE polymorphisms may denote increased sensitivity to dietary sodium. The alpha adducin gene is associated with increased renal tubular absorption of sodium and changes in this gene could be associated with hypertension. Genes encoding AT receptor, aldosterone synthase, atrial natriuretic peptide and beta-2 adrenoreceptor may also be associated with development of hypertension.

When the intake of Sodium Chloride(NaCl) exceeds the kidneys' capabilities to excrete it, the fluid in the vascular compartment increases, which in turn increases cardiac output transiently. However, over a period of time, the peripheral resistance increases, while the cardiac output reverts back to normal. NaCl can also activate neural, endocrine, paracrine and vascular mechanisms, all of which can increase arterial pressure. As

pressure rises in response to increased NaCl intake, the excretion of sodium increases concurrently. At this time, the body's sodium balance is now maintained by the higher arterial pressure, a phenomenon known as pressure natriuresis. Secondary causes of Hypertension include primary hyperaldosteronism, Cushing's syndrome, renovascular hypertension, coarctation of aorta and pheochromocytoma.

The emergence of resistant hypertension at an alarming rate has been a matter of concern. It is said to occur when there is failure to achieve blood pressure targets despite optimal doses of an appropriate three drug anti-hypertensive drug regimen which includes a diuretic. Poor compliance, excess sodium intake, kidney disease, inadequate doses of various drugs and excessive alcohol use may contribute to such a scenario. Furthermore, concomitant use drugs such as NSAIDs, COX-2 inhibitors, cocaine, cyclosporine and tacrolimus, erythropoietin and some over the counter diet supplements can also cause resistant hypertension<sup>1,2</sup>.

With a steep rise in the incidences of obesity and diabetes mellitus in the Indian subcontinent in the past decade, hypertension was a major co-habitant disease contributing to considerable morbidity in our country. There are some key differences to Hypertension in Asia, as compared to the west<sup>3</sup>. These include a steeper association of elevated blood pressure with stroke, greater salt sensitivity, ongoing obesity and metabolic syndrome epidemic, greater prevalence of stroke as compared to coronary artery disease in patients with hypertension.

Accurate measurement is paramount to accurate diagnosis and optimum monitoring<sup>4</sup>. Tight clothing must be removed, the patient must be allowed to rest for at least 5 minutes and the arm must be supported at heart level. Other patients include 24 hours' ambulatory blood pressure monitoring<sup>2,5,6</sup> (with a cut-off of 135/85 mmHg during the day and 120/75 mmHg at night), home blood pressure monitoring and impedance cardiography<sup>2</sup>.

## **II. Aims And Objectives**

Hypertension may well be one of the commonest cause for an outpatient's visit to a physician's office in our country. This condition is omnipresent and transcends regional, social and national boundaries. We set out to investigate the most common anti-hypertensive medication combinations used in an urban Indian population. We compared our results with five major independent international guidelines (published in the past six years) to assess what fraction of the Indian population was being treated according to guidelines. Our study participants had been diagnosed at various suburban and rural centers. The objective was to assess what portion our study population (and subsequently the Indian population, after questions of extrapolation have been addressed) was on the anti-hypertensive medication recommended by contemporary guidelines.

## **III. Methods**

We studied the 1081 asymptomatic patients previously diagnosed with essential hypertension on medication. These patients had been on medication for a mean duration of 30 months (25 to 36 months with a 95% CI). We analyzed the antihypertensive pharmacotherapeutic profile of these patients and conducted a single center, cross sectional, observational study, wherein the anti-hypertensive medications of these patients were grouped into various categories and compared against various existing guidelines. No attempt was made to change the medication the patients were on. Dose titration was, however, done on a case to case basis, as per standard practice. All patients were evaluated with a baseline hemogram and biochemistry, renal Doppler, lipid profile, thyroid profile, electrocardiogram and two-dimensional echocardiography with a view to rule out secondary causes.

**Inclusion Criteria:** All asymptomatic adult patients who presented to our outpatient department (generally on follow-up or for refill of medication) with a diagnosis of essential (primary) hypertension were included in the study. Many of these patients were diagnosed previously at other centers and were following up at our center. This is being reiterated to emphasize the fact that we make every attempt to initiate every patient on medication that is based on best available evidence. This cross sectional observational study is a platform to assess the existing pharmacotherapy that an urban Indian population is exposed to, with a view to examine such a pharmacotherapy's relevance and accuracy.

**Exclusion Criteria:** Patients with a discernible secondary cause of hypertension (reno-vascular hypertension, primary hyperaldosteronism, Cushing's disease, coarctation of aorta and thyroid disorders) were excluded. Patients with co-existing diabetes had to be excluded since their pharmacotherapeutics would be biased towards ACE inhibitors, and rightly so. Similarly, medications in patients with chronic kidney disease, previous coronary syndromes, cerebrovascular events would not reflect the first line choices made for hypertension in general clinical practice.

### Statistical Analysis

Frequency distribution of age showed that 9.1 % were in the 31-40 age group; 26.8 % (22.5-28.2 with 95% CI) in 41-50 years, 23.0% (20.1-24.6 with 95% CI) in the 51-60 years' group; 25.0%(22.3-27.2 with 95% CI) in the 61-70 years' group and 16.2 % (14.5-18.2 with 95% CI) in the 71-80 % group. While not powered to assess prevalence, this data shows that up to one in ten of all patients with hypertension are in the 31-40 years' age group. This has considerable ramifications for a developing country like India. The 95% confidence interval for population percent was calculated for the various drug combinations, namely, CCB alone, CCB and beta blockers, diuretics alone, ARB and diuretics and others.

### IV. Results

The results have been tabulated in [Table 1](#). Of the 1081 patients studied, 38.4% (35.5 – 41.3 with 95% CI) were on calcium channel blockers alone. This was most commonly found to be amlodipine, nifedipine or nicardipine. 30.0 % (27.2 – 32.7 with 95% CI) were on a combination of calcium channel blockers and beta blockers. This was mostly a CCB with atenolol or metoprolol. We had already excluded patients with prior MI, coronary artery disease or migraine. Inclusion of this demographic would have resulted in a significantly larger fraction of patients on Beta blockers. 14.1 % (12.09 – 16.25 with 95% CI) were on diuretics alone, 15.09% (12.96 – 17.23 with 95% CI) and 2.31 % (1.42 – 3.21 with 95% CI) were on other medication which includes beta blockers alone, alpha blockers alone and vasodilators.

### V. Discussion

Nine classes of anti-hypertensive drugs have been approved, which include thiazide type diuretics (chlorthalidone and hydrochlorothiazide), loop diuretics (furosemide and bumetanide), potassium sparing diuretics (triamterene and amiloride), antagonists of mineralocorticoid receptors (spironolactone and eplerenone), calcium channel blockers (amlodipine, felodipine, verapamil, diltiazem), beta blockers (metoprolol, atenolol, bisoprolol and esmolol), inhibitors of renin angiotensin system, alpha blockers (methyldopa, clonidine and guanabenz) and vasodilators (hydralazine and minoxidil).

Numerous countries around the world have issued their own guidelines for the management of essential hypertension. These include France<sup>7</sup>, Spain<sup>8,9</sup>, Japan<sup>10</sup>, China<sup>11</sup>, Croatia<sup>12</sup>, Japan, Taiwan<sup>13</sup>, Canada<sup>14,15</sup> and the United States<sup>4,16</sup>, to only name a few. The most recent guidelines are detailed in [Table 2](#). Back in 2014, the Joint National Committee (JNC 8) published guidelines for the management of essential hypertension<sup>5,17,18</sup>. This often-quoted reference in the management of hypertension stated clearly (in recommendation 6) that the first line drug for patients with recently detected hypertension could be a thiazide diuretic, a calcium channel blocker, an ACE inhibitor or an angiotensin receptor antagonist. Systolic targets to start anti-hypertensives in our study population (adults with no co-morbidities) was between 140 mm Hg (for patients younger than 60 years) and 150 mmHg (for patients 60 years or older). Diastolic targets remained 90 mmHg for both age groups. While the JNC 8 guidelines merit due consideration for its quality of evidence from numerous randomised controlled trials, it is not without critique. For starters, results from the Systolic Blood Pressure intervention trial was in contradiction to JNC 8 recommendations and showed an increased benefit from stringent blood pressure control (120/80 mmHg)<sup>19</sup>. However, the strength of evidence in the JNC 8 guidelines come from more than 30 RCTs and should be enough for the time being to hold its own.

The American society of hypertension guidelines from 2014, recommend similar targets, with the recommended drugs being the same. The only difference in the ASH/ISH guidelines are a more generous age cut off of 80 years. The American Heart Association guidelines suggest a more conservative target of 140/90 mmHg and recommend first line therapy with thiazine diuretics (evidence from randomised controlled trials recommend the use of Chlorthalidone, rather than Hydrochlorothiazide).

The European society of hypertension<sup>20</sup> and the Canadian Hypertension Education Program<sup>14,21</sup> recommended the use of beta blockers as first line therapy, however our experience shows that while beta blockers are excellent open options in patients with present or previous coronary heart disease or failure, there is insufficient evidence to recommend their use as first line therapy, since they have limited efficacy unless prescribed with CCBs or diuretics. This is in accordance with the other abovementioned guidelines. Furthermore, the LIFE trial demonstrated equal efficaciousness between Beta blockers and ARBs, thereby paving the way for the latter as a first choice, with a definitively better adverse effect profile.

The cross-sectional analysis in our study shows that most of the study population was on medication for essential hypertension as per the best existing guidelines. One in three patients in the study population was on a combination containing beta blockers, which is in accordance with the CHEP and ESH guidelines, but not according to the JNC 8 guidelines or other more recent guidelines. This probably demonstrates a therapeutic lag, an inertia to embrace the more recent guidelines which, the authors feel, is partly due to the efficacy of the beta blockers in producing a therapeutic response, especially in combination with other first line anti-hypertensive

drugs. Therefore, prescriptions of beta blockers are certainly not inappropriate. However, the presence of better drugs, based on meta-analysis of several trials makes their indiscriminate use a cause of concern.

## VI. Conclusion

Hypertension is one of the foremost causes of morbidity in the modern world. The responsibility for accurate diagnosis and management lies with all health care providers in our country. The authors are pleased to note that most of the study population was being managed in accordance with the latest guidelines. The authors also realise that the data in this study was not powered enough to be able to extrapolate the results on to the Indian population. However, the study does provide an insight into current pharmacotherapeutic practices in our country for common medical conditions. Larger studies and therapeutic flexibility to keep pace with rapidly changing guidelines is the need of the hour.

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**Table 1 – Results**

Year	Guideline	Age	Office Threshold	Initial Drug Options
2014	JNC <sup>8</sup>	>60 Years <60 Years	>150/90 >140/90	Thiazide, ACEI Or ARB, CCB
2014	ASH/ISH <sup>#</sup>	>80 Years <80 Years	>150/90 >140/90	Thiazide, ACEI Or ARB, CCB
2013	AHA/ACC/CDC <sup>&amp;</sup>	General	>140/90	Thiazide, ACEI Or ARB, CCB
2013	ESH/ESC <sup>@</sup>	>80 Years 60-79 Years <60 Years	>160/90 >150/90 >140/90	Thiazide, Beta Blocker, CCB, ACEI Or ARB
2013	CHEP <sup>^</sup>	>80 Years <80 Years	>150/90 >140/90	Thiazide, Beta Blocker, CCB, ACEI Or ARB
* Joint National Committee				
# American Society Of Hypertension/International Society Of Hypertension & American Heart Association				
@ European Society Of Hypertension				
^ Canadian Hypertension Education Program				
ACEI- Angiotensin Converting Enzyme Inhibitor				
ARB- Angiotensin Receptor Blocker				
CCB- Calcium Channel Blocker				

**Table 2 – Recent Guidelines For Management Of Hypertension**

Therapy	Frequency	Percent	95% Confidence Interval for Population Proportion	Interpretation
CCB alone	415	38.43	(35.52%, 41.33%)	The population proportion of patients with CCB alone is between (35.52%, 41.33%) with 95% confidence.
CCB & BB	324	30.00	(27.27%, 32.73%)	The population proportion of patients with CCB & BB is between (27.27%, 32.73%) with 95% confidence.
Diuretic alone	153	14.17	(12.09%, 16.25%)	The population proportion of patients with Diuretic alone is between (12.09%, 16.25%) with 95% confidence.
ARB & Diuretic	163	15.09	(12.96%, 17.23%)	The population proportion of patients with ARB & Diuretic is between (12.96%, 17.23%) with 95% confidence.
Others	25	2.31	(1.42%, 3.21%)	The population proportion of patients with Others is between (1.42%, 3.21%) with 95% confidence.