

ARTICLE



A multi-centre study of prescribing patterns for the management of resistant hypertension amongst cardiologists

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Resistant hypertension is conventionally defined as failure to achieve blood pressure control despite treatment with optimal or maximally tolerated doses of three antihypertensive drugs, typically including a renin–angiotensin system blocker, a calcium channel blocker, and a diuretic. In real-world practice, however, many patients receive four or more antihypertensive agents without necessarily fulfilling classical resistant hypertension criteria, and data describing such prescribing patterns among cardiologists are limited. We conducted a prospective, multicentre, cross-sectional observational study across 10 cardiology outpatient centres enrolling consecutive adult patients (≥ 18 years) receiving more than three antihypertensive drugs. Patients with renal denervation, renal transplantation, known renal artery stenosis, or incomplete data were excluded. Demographic characteristics, blood pressure, comorbidities, and antihypertensive prescriptions were recorded, with a predefined analysis of mineralocorticoid receptor antagonist (MRA) use in the overall cohort and in patients meeting guideline criteria for resistant hypertension. A total of 420 patients were included (mean age 65.2 years; male-to-female ratio 1:0.8). Renin–angiotensin system inhibitors, calcium channel blockers, and diuretics were prescribed in 89, 85, and 82% of patients, respectively, while beta-blocker use was high at 85%. Overall MRA use was low at 39%. Among patients fulfilling criteria for resistant hypertension ($n = 273$), MRA use was 27%, increasing to only 38% when serum potassium was ≤ 4.5 mEq/L. Serum potassium ≤ 4.5 mEq/L was the only independent predictor of MRA prescription. These findings highlight substantial underutilization of MRAs in real-world practice and an important opportunity to improve guideline-directed management of resistant hypertension.

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The fifth National Family Health survey (NFHS-V) found that the prevalence of systemic hypertension (HTN) was 22.6% in India. The prevalence of HTN in the urban and rural population were 25 and 21.4% respectively [1]. The control rate of hypertension ranged between 10 and 25%. Most of the major HTN trials required more than two drugs for the control of hypertension.

Resistant HTN is defined as failure to achieve a blood pressure (BP) of $< 140/90$ mm Hg despite the use of optimal or maximally tolerated doses of a renin angiotensin system inhibitor (RAASi), a calcium channel blocker (CCB) and a diuretic (thiazide or thiazide-like) [2]. The overall prevalence of resistant Hypertension is 10–20%. Following the three drugs, the fourth drug is usually a mineralocorticoid receptor antagonist (MRA) when the serum potassium is < 4.5 mEq/L [3]. Evidence for MRAs as fourth-line therapy stems from PATHWAY-2 trial, where spironolactone reduced BP by 8.7 mm Hg, more than alternatives in resistant hypertension ($p < 0.001$). In accordance with this evidence, guideline recommendations endorse MRAs as the preferred fourth-line agent when serum $K^+ \leq 4.5$ mEq/L [4]. However, in real-world practice, this is seldom followed, and in general, the use of beta-blockers has been very high among Indians, since the

resting heart rate among Indians is higher [5]. A study of the prescription pattern of antihypertensive medication among 395 patients did not record a single patient on MRA [6]. Another study on diabetic subjects had similar findings [7]. There is no large study on the pattern of antihypertensive drug use among cardiologists in real-world with unrestricted use of medication.

Although the classical definition of resistant hypertension requires the use of a renin–angiotensin system blocker, calcium channel blocker, and a diuretic at optimal doses, the present study deliberately included all patients receiving more than three antihypertensive drugs to capture real-world prescribing patterns among cardiologists, including apparent and true resistant hypertension.

METHODOLOGY

The study design was a prospective, multicentric cross-sectional observational study at outpatient cardiology facilities. Adult hypertensive patients were consecutively recruited from outpatient clinics across 10 cardiology centres to minimize selection bias. All the patients who were on more than three

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Table 1. Demographic and Clinical Data of the Study.

Parameter	Metrics
Mean Age	65.18 + /− 11.15 years
Male:Female ratio	01:00.8
Duration of Hypertension	14.23 + /− 8.61 years
Mean Office Systolic Blood pressure	143.58 ± 16.95
Mean Office Diastolic Blood pressure	78.93 ± 12.96
Mean Office Pulse rate	78.47 ± 12.58
Smoking	9 (2%)
Asthmatic	25 (6%)
Type 2 Diabetes	270 (64%)
Hypothyroidism	65 (15%)
Hyperthyroidism	1
Underlying Ischemic Heart Disease	190 (45%)
Snoring/Obstructive sleep apnoea	64 (15%)
Left ventricular hypertrophy by echo	321 out of 407 (79%)
Regular physical activity	319 (76%)
Regular salt restriction	366 (87%)
Home blood pressure monitoring	282 (67%)

antihypertensive medications were included. Patients with post renal denervation status, post renal transplantation, renal artery stenosis and incomplete data were excluded. Secondary causes, including concurrent NSAID use, were not systematically excluded via screening tests due to the real-world observational design; however, clinical judgment by cardiologists ensured typical resistant hypertension cases, with exclusions for known renal artery stenosis. Ethics Committee approval was secured from two institutions. An informed consent was obtained from all enrolled patients. Comorbidities were captured. Office blood pressure and pulse rate were recorded. The details of all the medication including dose were recorded. Since this was a cross-sectional study, no follow up was planned. The data was collected and tabulated in Microsoft Excel and analyzed by a statistician using SPSS software.

After discerning the overall pattern of drug usage, the use of MRAs was corroborated with serum potassium levels with a cutoff value ≤ 4.5 mEq/L in the overall group and specifically in those patients who were on RAASi, CCB and diuretics (fitting into the diagnosis of Resistant Hypertension). The association between serum potassium levels (cutoff of ≤ 4.5 mEq/L) and MRA (Mineralocorticoid Receptor Antagonist) prescription was assessed using the Chi-square test. The binary logistic regression model included the variables Age, Sex (Male), Duration of Hypertension, Diabetes Mellitus (DM), Left Ventricular Hypertrophy (LVH), Serum Creatinine, and Serum Potassium (categorized as cutoff at 4.5). The dependent variable was whether MRA was prescribed or not.

RESULTS

Ten outpatient cardiology centers were selected and patients enrolled. Out of 427 patients whose data were available, 7 were excluded due to incomplete data and 420 patients were used for final analysis. The mean age was 65.2 years with a male-to-female ratio of 1: 0.8. The duration of HTN was 14.26 + /− 8.26 years. The overall demographic and clinical parameters are given in Table 1.

The Mean Recorded BP was 143/79 + /− 17/13 mm Hg. Type 2 diabetes mellitus was present in 270 (64%) while 190 (45%) had underlying ischemic heart disease. History of snoring or known obstructive sleep apnea was noted in 65 persons (15%). Left ventricular hypertrophy was recorded by echocardiography in 321

Table 2. Pattern of drug use when more than three drugs are used for the control of hypertension.

Drug Class	Number of patients	Percentage of patients
Angiotensin Converting Enzyme inhibitors	3	1%
Angiotensin Receptor blocker	369	88%
Calcium channel blocker	359	85%
Diuretic	345	82%
Betablocker	359	85%
Mineralocorticoid receptor antagonist	164	39%
Hydralazine	107	25%
Clonidine	8	2%
Moxonidine	39	9%
Sustained release prazosin	107	25%
Minoxidil	6	1%

out of 407 persons with a recorded echocardiogram (79%). Regular physical activity, and salt restriction at 319 (76%), and 366 (87%) respectively were noted. Majority of the patients 282 (67%) were on home blood pressure monitoring.

The pattern of drug use is summarized in Table 2. And the graphical representation is given in Fig. 1.

The three most commonly used antihypertensive drug classes were angiotensin receptor blockers (88%), calcium channel blockers (85%) and diuretics (82%). Beta-blocker use was a very high 85%. The proverbial fourth drug, the MRA, was prescribed in only 39% of patients. Hydralazine and extended-release prazosin were prescribed at 25% each. The other drugs used were moxonidine (9%), clonidine (2%), minoxidil (1%) and angiotensin converting enzyme inhibitor (1%).

MRA ANALYSIS

The association between serum potassium levels (with cutoff of 4.5mEq/L) and MRA (Mineralocorticoid Receptor Antagonist) prescription was assessed using the Chi-square test. A serum potassium estimation was available in 347 patients. While the overall prescription of MRA was 39%, the prescription among patients with serum potassium value ≤ 4.5 and >4.5 mEq/L were 48 and 33% respectively. Among patients who were prescribed an MRA, 76.2% (n = 115) had serum potassium levels ≤ 4.5 mEq/L, while 23.8% (n = 36) had potassium levels >4.5 mEq/L. In contrast, among those not prescribed MRA, 63.3% (n = 124) had serum potassium levels ≤ 4.5 mEq/L and 36.7% (n = 72) had levels >4.5 mEq/L. Overall, 68.9% of the entire sample had potassium levels ≤ 4.5 . The Pearson Chi-square test showed a statistically significant association between serum potassium levels and MRA prescription ($\chi^2 = 6.614$, df = 1, p = 0.010). This indicates that individuals with lower serum potassium (≤ 4.5) were significantly more likely to be prescribed an MRA compared to those with higher potassium levels.

The binary logistic regression model included the variables Age, Sex (Male), Duration of Hypertension, Diabetes Mellitus (DM), Left Ventricular Hypertrophy (LVH), Serum Creatinine, and Serum Potassium (categorized as cutoff at 4.5 mEq/L). The dependent variable was whether MRA was prescribed or not. Among the aforementioned variables studied, only Serum Potassium ≤ 4.5 mEq/L was found to be a statistically significant predictor of MRA prescription. The results are given in Table 3. Other demographic and clinical variables did not independently predict MRA use in this model.

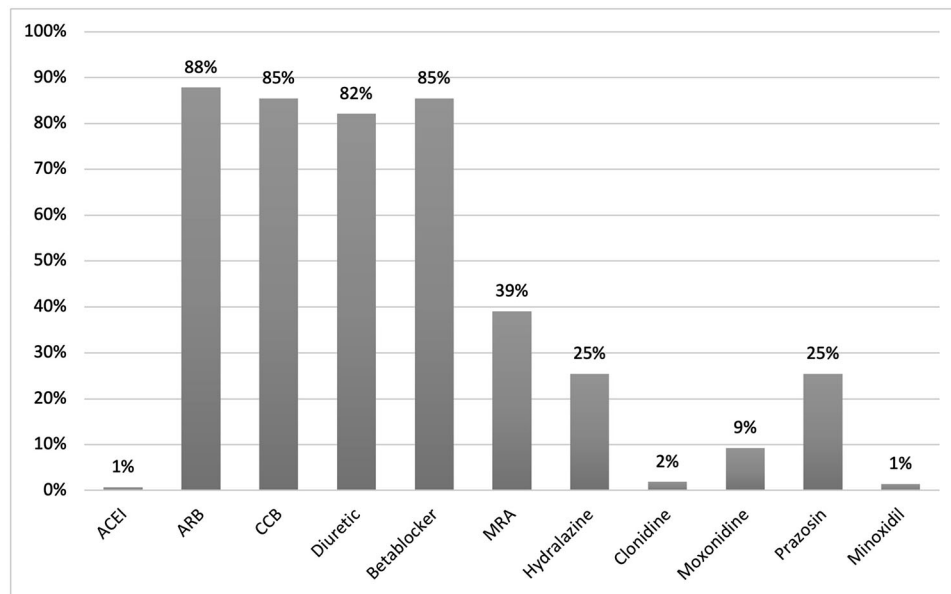


Fig. 1 Pattern of drug use among patients receiving $\geq$ four antihypertensive medications.

Table 3. Results of the binary logistic regression model with prescription of MRA as the dependent variable.

Variable	B	S.E.	Wald	df	P value	Odds Ratio	95% upper CI	95% lower CI
Age	−0.021	0.011	3.702	1	0.054	0.98	0.959	1
Male(1)	0.398	0.231	2.964	1	0.085	1.489	0.946	2.341
DurationofHT	0.003	0.014	0.038	1	0.845	1.003	0.976	1.03
DM(1)	0.136	0.241	0.317	1	0.573	1.145	0.715	1.836
LVH_A(1)	0.213	0.231	0.852	1	0.356	1.237	0.787	1.944
Creatinine	0.018	0.021	0.767	1	0.381	1.018	0.978	1.061
SerumPotassiumCutoff4.5	−0.565	0.254	4.951	1	0.026	0.568	0.346	0.935
Constant	1.344	0.704	3.648	1	0.056	3.836		

Out of the total 420 persons, 273 (65%) were on all three drugs (RAASi + CCB + Diuretic) to qualify for resistant HTN. MRA use in this subset was 27% (75 out of 273 persons). Seventy persons had a recent (< 1 month) serum potassium recorded. In this subgroup, when serum potassium was ≤ 4.5 mEq/L, 38% were on MRAs and when serum potassium was > 4.5 mEq/L it was 18%.

DISCUSSION

Multiple drugs are required for the control of HTN. Data and rationale on the use of antihypertensive medication among cardiologists in real-world has not been studied. The present study is one of the largest real-world multicentre observational studies to evaluate prescribing patterns of antihypertensive polypharmacy among cardiologists.

ARBs are the preferred drug (88%) while only 1% were on ACEI. One possible explanation is the perception among cardiologists that ARBs are better tolerated and more effective – this will need a separate survey among the participating cardiologists, which is planned based on the results. Dhanraj et al studied polypharmacy in HTN of whom 37 persons were on ≥ 4 drugs. ARB use was 97%, while the use of CCB (92%), diuretic (81%), ACEI (78%) and BB (65%) were also high. With 97% on ARBs and 78% on ACEI, several patients were on combined ACEI and ARBs [7]. This study was published in 2012, much later than the ONTARGET trial (published in 2008) which highlighted the harmful effects of combining ACEI and ARBs [8]. A study on the pattern of hypertensive drug use in a tertiary care

hospital in India ($n = 200$) had only 19 persons on four drugs. All the persons were on a combination of ARB, CCB, Diuretic and BB [6].

Binary logistic regression analysis of Age, Sex (Male), Duration of Hypertension, Diabetes Mellitus (DM), Left Ventricular Hypertrophy (LVH), Serum Creatinine, and Serum Potassium (categorized as cutoff at 4.5 mEq/L), reiterated the recommendation of using MRA when serum potassium levels are ≤ 4.5 mEq/L [3].

Among the subset of patients who qualified for the definition of resistant HTN ($n = 273$), 27% were on MRAs. When serum potassium was ≤ 4.5 mEq/L, only 38% were on MRAs, implying that the MRA use among cardiologists was not strictly governed by serum potassium levels. The two studies from India do not even mention the use of MRAs [6]. Literature search on the real-world prescription pattern in HTN showed six studies with some patients on more than three drugs for the control of HTN. Most prior real-world studies evaluating antihypertensive polypharmacy were small or heterogeneous and provided limited data on MRA use. The comparative details are given in Table 4 [9–13].

Beta-blocker use among cardiologists was very high at 85%. Previous studies in India have shown that the resting heart rate is higher and this could be a possible explanation for the high use of BB. In Narkar et al data 47% were on BB, and in Dhanaraj et al data 64% were on BB [6, 7].

Comparing the global data on the real-world polypharmacy in HTN, the Pol-Focus study had 3060 patients with resistant HTN wherein RAASi, CCB, diuretics and BB were prescribed in 96.4, 54, 80 and 74% respectively. MRA use was only 15% [9]. This

Table 4. Prescription pattern when four or more drugs were used to treat systemic hypertension.

Study	Number of patients on ≥ 4 drugs	RASI*	CCB [#]	Diuretic	BB [†]	MRA [‡]	MRA in Resistant HTN
Alkaabi et al. [9]	48	97%	81%	100%	94%	31% on two diuretics	39 persons 3 on two diuretics (8%)
Shastry et al. [10]	6	100%	100%	100%	100%	-	-
Tandon et al. [11]	5	100%	100%	100%	100%	-	-
Dhanaraj et al. [7]	37	97%	92%	81%	65%	-	-
Bulatova et al. [12]	75					Overall 14%**	
POL-Focus study [13]	3060	96%	54%	80%	74%	15%	
Present study	420	89%	85%	82%	85%	39%	27%

*-renin angiotensin systemic hypertension inhibitors.

[#]- calcium channel inhibitors.

[†]- betablockers.

[‡]-mineralocorticoid receptor antagonists.

[¶]- hypertension.

**-overall 14% were on potassium sparing diuretics, with individual details not shared.

highlights some important facts from the present study (i) The use of the conventional first line three drugs namely the RAASi, CCBs and diuretics is high at 89, 85 and 82% respectively. (ii) the Use of BB is 85% which is also high and could possibly highlight the fact that the basal heart rate in Indians is higher. (iii) Overall MRA use was low at 39%. While MRA prescription increased to 48% among patients with serum potassium levels ≤ 4.5 mEq/L, utilization remained suboptimal, underscoring persistent underuse. Nevertheless, serum potassium ≤ 4.5 mEq/L was the only significant correlate of MRA prescription.

Limitations of the study are (i) cross-sectional study and not longitudinal to assess the response (ii) compliance of drugs is not confirmed (iii) secondary causes of hypertension were not methodically ruled out since this is a real-world cross-sectional study (iv) serum potassium was not done in all the patients (although this is a real-world study) (v) BP control was not assessed to look at the response (this was not the aim of the study).

To conclude, when more than three drugs were used to control HTN, cardiologists used BB (85%) while MRA use was just 39%. Serum potassium < 4.5 mEq/L was the only statistically significant predictor for the use of MRAs despite its gross underutilization.

Future guidance with a follow-up among the same group of investigators would determine if the message of underutilization of MRAs has reflected in clinical practice. Physician education on the awareness of the use of MRAs is the need of the hour.

SUMMARY

What is known about the topic?

- Resistant hypertension is conventionally defined as uncontrolled blood pressure despite treatment with a renin-angiotensin system blocker, a calcium channel blocker, and a thiazide or thiazide-like diuretic at optimal or maximally tolerated doses.
- Mineralocorticoid receptor antagonists (MRAs) are the preferred fourth-line agents based on robust trial and guideline evidence.
- Prior real-world studies evaluating antihypertensive polypharmacy are limited, heterogeneous, or small, and consistently suggest underutilization of MRAs.

What this study adds

- In a large, multicentre, real-world cohort of patients receiving four or more antihypertensive drugs ($n = 420$), cardiologists most frequently prescribed RAAS inhibitors (89%), calcium channel blockers (85%), and diuretics (82%).
- Beta-blockers were used in 85% of patients, indicating a high reliance on this drug class during antihypertensive polypharmacy.
- Overall MRA use was low (39%), despite guideline recommendations.
- Among patients meeting guideline criteria for resistant hypertension (RAAS inhibitor + CCB + diuretic; $n = 273$), MRA use was only 27, and only 38% when serum potassium was ≤ 4.5 mEq/L.
- These findings highlight a substantial evidence-practice gap and underscore the need to improve guideline-directed use of MRAs in resistant hypertension.

DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request. Individual participant data are not publicly available due to privacy and institutional ethical restrictions.

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AUTHOR CONTRIBUTIONS

All authors take responsibility for the integrity of the data and the accuracy of the data analysis. PD conceived the study and designed the research protocol. PD, SAN, AM, SKP, HP, IU and SS acquired the data and conducted the data analysis and interpretation. PD drafted the manuscript. SSS critically revised the manuscript for

important intellectual content. PD and SN performed statistical analyses. PD, SS and IU provided administrative, technical and material support and supervised the overall conduct of the study.

COMPETING INTERESTS

All the authors do not have any conflict of interest with the present study. There is no industry sponsorship for the study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Declaration of Helsinki and all relevant institutional and national ethical guidelines and regulations. Ethical approval was obtained from the institutional ethics committees of Billroth Hospitals (ECR/1761/Inst/TN/2023) and Dr.Mehta's Hospitals, Chennai (EC.MMHIPL/21/07/2021) Written informed consent was obtained from all participants prior to enrolment in the study.

ADDITIONAL INFORMATION

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