



# Difference in Antihypertensive Medication Pattern in the First Year Compared to More than a Year of Maintenance Hemodialysis: A Northern India Tertiary Care Experience

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Ann Natl Acad Med Sci (India) 2022;58:157–163.

## Abstract

**Introduction** There is a high prevalence of hypertension in maintenance hemodialysis patients. Information regarding prevalent pattern of antihypertensive medications will help modify it to prevent future cardiovascular morbidity and mortality.

**Materials and Methods** In this cross-sectional study, patients on maintenance hemodialysis, aged  $\geq 18$  years visiting Nephrology outpatient department (OPD) from April 2019 to May 2020 were included. The patients were divided into two groups based on their dialysis vintage,  $\leq 12$  months and  $> 12$  months. Their antihypertensive medication patterns and two-dimensional (2D) echocardiography (ECHO) findings were compared. Independent *t*-test was used to compare continuous variables. One-way analysis of variance was used to study the antihypertensive drug-dosing pattern in both the groups.

**Results** Out of 250 patients, 131 had a dialysis vintage of  $\leq 12$  months, whereas 119 had a vintage of  $> 12$  months. There was no significant difference in the number of antihypertensive agents used in either of the vintage groups. Calcium channel blockers (87.02 and 89.07%, respectively, in  $\leq 12$  and  $> 12$  months' vintage groups) and  $\beta$  blockers (64.12 and 65.54%, respectively, in  $\leq 12$  and  $> 12$  months' vintage groups) were the commonly used antihypertensive agents. Metoprolol use was higher in  $\leq 12$  months' group, whereas carvedilol usage was higher in  $> 12$  months' group ( $p = 0.028$ ). Mean pill burden was more than five in both the groups. Concentric left ventricular hypertrophy was significantly more common in  $> 12$  months' group. Renin-angiotensin system (RAS) blocking agent use was limited to 3% of patients.

**Conclusion** This study shows a high antihypertensive pill burden in dialysis patients likely due to underlying chronic volume overload in addition to the perceived efficacy of certain class of drug in a frequent dosing pattern. Low use of RAS blocking agent was also underlined. This study highlights the need to bring about changes in the antihypertensive prescription pattern in line with the existing evidence.

## Keywords

- ▶ hypertension
- ▶ antihypertensive medication
- ▶ hemodialysis

published online  
January 10, 2022

DOI <https://doi.org/10.1055/s-0041-1742140>.  
ISSN 0379-038X.

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Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

## Introduction

The prevalence of hypertension in patients on maintenance dialysis is quite high (>70%)<sup>1</sup> and varies depending on the defining criteria used. Managing hypertension in them requires a multitargeted approach. It starts with optimization of fluid status, lowering sodium intake to less than 3 gm/day and optimization of erythropoiesis stimulating agents. A sizeable number of these eventually require pharmacological therapy. Blood pressure (BP) lowering medications are known to reduce cardiovascular mortality.<sup>2,3</sup> Certain class of drugs have an advantage in terms of giving cardiovascular protection like renin-angiotensin system (RAS) blocking agents and  $\beta$ -blockers (BBs). The variation in treatment is expected to be high in the first year when exposure to dialysis fluid starts along with hemodynamic changes associated with the dialysis process. However, there is scarcity of data on the antihypertensive prescription pattern in the first and later years of maintenance hemodialysis. This holds true particularly in places where twice a week hemodialysis is virtually the norm. Understanding BP medication patterns is important to provide a guide to measures aimed at improving BP control, preserving residual renal function, and preventing cardiovascular mortality. It will go a long way in filling up the lacunae in our prescription pattern.

Hence, this study was undertaken to study the pattern of BP medications of patients in their first year of maintenance hemodialysis compared with the patients on hemodialysis for more than a year. The two-dimensional (2D) echocardiography (2DECHO) findings were also compared in the above groups.

## Materials and Methods

An observational cross-sectional study of all prevalent end-stage renal disease (ESRD) patients aged  $\geq 18$  years who were receiving hemodialysis for at least 3 months visiting an outpatient department (OPD) of Nephrology at this North Indian tertiary care hospital from April 2019 to May 2020. Only patients with stable BP prescription for at least 2 weeks were included. BP medication patterns, including the class, dose, and frequency, were recorded. BP readings (an average of two readings after 5 minutes of rest on a bare nonaccess arm manually using mercury sphygmomanometer) were obtained during the routine OPD visit on nondialysis days. 2D ECHO was performed by cardiologist on nondialysis days. Baseline characteristics, including age, sex, laboratory, clinical data and dialysis prescription were obtained.

Exclusion criteria were patients on hemodialysis for less than 3 months and/or history of hospitalization within 2 months from the time of being included in the study. Patients with incomplete data or documented non adherence to the treatment regimen were also excluded.

All the data were retrospectively obtained from the hospital information system. The patient were then divided into two groups based on the dialysis vintage, that is,  $\leq 12$  and  $> 12$  months.

The antihypertensive pill burden was defined as the total number of antihypertensive pills the patients took on a daily basis.<sup>4</sup> Adherence to the antihypertensive therapy was checked via the electronic recordings made in the hospital information system.

Interdialytic weight gain was defined as the increase in body weight from the clinically derived postdialysis dry weight of the patient. Target dry weight in this study was based on clinical assessment determined by patient's tolerance to fluid removal without intradialytic symptoms and hypotension along with absence of overt fluid overload. An average of last 2-week readings was taken. The adequacy of dialysis (Single-pool Kt/Vurea) was assessed by the dialysis records.

The dialysate concentration of sodium used in the patients was between 135 and 136 mEq/L.

## Statistical Analyses

Statistical analyses were performed using the SPSS version 20.0 (SPSS, Chicago, Illinois, United States). We used descriptive statistics (mean  $\pm$  standard deviation [SD]) for continuous variables. Independent *t*-test was used to compare continuous variables. Chi-square was used to compare categorical variables between the two groups. The one-way analysis of variance (ANOVA) was used to determine any statistically significant difference between the drug dosing pattern of various antihypertensive agents.

## Results

Out of a total of 423 patients screened, after application of inclusion and exclusion criteria, 250 hemodialysis patients were included in our study. A total of 131 patients had a vintage of  $\leq 12$  months, whereas 119 had a vintage of  $> 12$  months (► **Table 1**). The patient population was young (mean age:  $42.36 \pm 13.73$  years) and comprised of higher number of males (192 [76.8%]). In both the groups, diabetes mellitus was the most common comorbidity. There was no significant difference in interdialytic weight gain between both the groups ( $2.45 \pm 0.95$  kg. in  $\leq 12$  months' and  $2.67 \pm 0.96$  kg. in  $> 12$  months' groups, respectively;  $p = 0.07$ ). Hemoglobin was suboptimal in both the groups. It was significantly higher in  $> 12$  months' vintage group as compared with  $\leq 12$  months' vintage group ( $9.48 \pm 1.33$  and  $8.47 \pm 1.66$  g/dL, respectively,  $p < 0.01$ ). Both the groups did not significantly differ in their dialysis adequacy.

### Comparison between $\leq 12$ and $> 12$ Months' Vintage Groups

Number of BP medications and prescription patterns: 55.37% of patients were on at least three or four antihypertensives. There was statistically no significant difference in the number of antihypertensive agents used in either of the vintage groups.

Calcium channel blockers (CCBs) were the most commonly used antihypertensive agents (87.02 and 89.07% in  $\leq 12$  and  $> 12$  months' vintage groups, respectively) followed by

**Table 1** Baseline clinical and laboratory characteristics

	≤12 months (n = 131)	>12 months (n = 119)	p-Value
Age (y)	41.95 ± 14.52	42.70 ± 12.64	0.67
Sex	M = 101; F = 30	M = 88; F = 31	0.51
Vintage (mo)	6.11 ± 6.07	30.62 ± 13.31	0.001
Comorbidities	T2DM = 54, hypothyroidism = 24, CLD = 4, COPD = 1	T2DM = 42, hypothyroidism = 4, CAD = 5, CLD = 5, COPD = 3	
Basic disease	DKD = 52, CGN = 38, CIN = 21, unknown = 18	DKD = 40, CGN = 12, CIN = 40, unknown = 27	
Weight (kg)	56.13 ± 9.87	52.47 ± 10.55	0.003
Interdialytic weight gain (kg)	2.45 ± 0.95	2.67 ± 0.96	0.07
BP systolic (mm Hg)	142.97 ± 14.41	144.30 ± 14.79	0.59
BP diastolic (mm Hg)	86.23 ± 7.63	84.06 ± 8.66	0.06
Hb (g/dL)	8.47 ± 1.66	9.48 ± 1.33	<0.01
Urea (mg/dL)	120.94 ± 43.56	128.1 ± 37.50	0.20
Serum creatinine (mg/dL)	8.97 ± 2.54	9.61 ± 2.61	0.07
Serum sodium (mEq/L)	134.96 ± 4.98	133.76 ± 17.6	0.48
Serum potassium (mEq/L)	5.11 ± 1.67	5.22 ± 0.38	0.55
Serum calcium (mg/dL)	8.55 ± 1.08	8.68 ± 1.0	0.39
Serum albumin (g/dL)	3.40 ± 0.59	3.77 ± 0.57	0.00
Serum phosphorus (mg/dL)	5.89 ± 1.86	5.68 ± 1.65	0.42
iPTH (pg/mL)	338.03 ± 273.26	326.86 ± 310.54	0.79
Sp Kt/V	1.4 ± 0.3	1.5 ± 0.5	0.11
2D echocardiographic findings			
Ejection fraction	54.21 ± 8.41	48.9 ± 11.4	0.15
RWMA	8	6	0.42
Concentric LVH	85	96	0.005
Diastolic dysfunction	46	52	0.08
Valvular dysfunction			
TR	25	33	0.10
MR	10	7	0.53
TR + MR	23	28	0.24
AS	1	3	0.36
AR	3	4	0.79
TR + MR + AR	9	5	0.35
TR + AR	1	1	

Abbreviations: 2D, two-dimensional; AR, aortic regurgitation; AS, aortic stenosis; BP, blood pressure; CAD, coronary artery disease; CGN, chronic glomerulonephritis; CIN, chronic interstitial nephritis; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; DKD, diabetic kidney disease; F, female; Hb, hemoglobin; iPTH, intact Parathyroid Hormone; LVH, left ventricular hypertrophy; M, male; MR, mitral regurgitation; RWMA, regional wall motion abnormality; Sp Kt/V, Single-pool Kt/Vurea; T2DM, type 2 diabetes mellitus; TR, tricuspid regurgitation.

BBs (64.12 and 65.54% in ≤12 and >12 months' vintage groups, respectively; - **Table 2**).

Among CCBs, amlodipine was the most commonly used one in both the groups. Metoprolol was the most common BB to be used in ≤12 months' group and its usage was significantly more than the >12 months' group. ( $p = 0.028$ ). Carvedilol was the most common BB used in >12 months' duration group which was also significantly

higher than the ≤12 months' group ( $p = 0.013$ ). Use of RAS blocking agents use was reported in approximately 3% of patients.

As far as formulation is concerned, nifedipine in the slow release preparation (retard) and succinate formulation of metoprolol were used in the subjects. Torsemide was the lone loop diuretic used. Among thiazides, only metolazone was used.

**Table 2** Antihypertensive class wise distribution

	≤12 months (n = 131)	>12 months (n = 119)	p-Value
ACEI/ARBs Telmisartan	4 4	3 3	0.253
Calcium channel blockers	114	106	0.760
Amlodipine	58	52	0.892
Cilnidipine	12	12	0.887
Nifedipine	42	40	0.842
(retard)	02	00	0.614
Benidipine			
β-blockers	84	78	0.911
Carvedilol	30	44	0.013
Metoprolol	50	32	0.028
succinate	02	02	0.940
Atenolol	02	00	0.435
Nebivolol			
Central α-2 agonist	74	76	0.264
Clonidine	74	76	
α-blockers	42	36	0.707
Prazosin (XL)	42	36	
Diuretics	56	28	0.010
Torsemide	50	28	0.177
Thiazide	06	00	
Direct vasodilators	00	06	0.010
Minoxidil			
Aldosterone antagonists	02	00	
Spironolactone			
Mean number of antihypertensive drugs	2.90 ± 1.50	2.84 ± 1.41	0.65
Combination used	28	14	0.037

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

No significant difference by sex or comorbidities in type and number of antihypertensives used was seen.

Mean dose of α-blocker was significantly higher in >12 months' compared with ≤12 months' group ( $p < 0.001$ ; ► **Table 3**). Higher dose of loop diuretic was used in >12 months' group, albeit nonsignificant. No significant difference in overall BP (both systolic and diastolic) control was seen in both the groups.

No significant difference in terms of interdialytic weight gain was seen in both the groups.

Combination BP medications: the only prevalent combination used was that of CCBs and BBs. Use of combination medications was significantly higher in ≤12 months' category ( $p = 0.037$ ).

The antihypertensive pill burden was similar in both the groups (► **Fig. 1**). Central α-2 agonists contributed most to the pill burden as they were mostly used in thrice daily

regimen (► **Table 4**). Eight (3.2%) patients were not on any antihypertensive agent.

### Two-Dimensional Echocardiography Findings

Left ventricular hypertrophy was significantly more in >12 months' vintage group than ≤12 months' vintage group (80.7 and 64.9%, respectively;  $p = 0.005$ ). Diastolic dysfunction was seen in 39% of the patients with no significant difference between the groups (► **Table 1**).

Tricuspid regurgitation and mitral regurgitation were the most common valvular defects in both the groups.

### Discussion

As there is lack of clarity and uniformity in the use of antihypertensives in dialysis patients, the current study brings into picture the prevalent practice pattern of BP medications. This study is significant as mortality is particularly high in the initial months of dialysis which may be due to several patient (age, catheter vascular access issues, and malnutrition) and treatment-related factors.<sup>5</sup> Hypertension is an important modifiable cardiovascular risk factor. Details of prescription pattern of these drugs will help modify it in line with the existing evidence.

Our study compares the BP medication patterns in hemodialysis patients with ≤12 months and >12 months of dialysis vintage. Our study revealed a high pill burden and requirement of multiple antihypertensive agents in both the groups. In terms of class of agents, CCBs were the most common ones to be used. Usage of RAS blockers was dismal. Also, >12 months' group of patients required a higher dose of diuretics. Overall, BP control was similar in both the groups. We hypothesized that the mean number of BP medications would increase over time after 1 year on dialysis as residual renal function is lost and patients often find it difficult to titrate fluid intake accordingly, along with worsening vascular stiffness.<sup>5</sup> They often continue to take more than recommended fluids resulting in increase of the need for ultrafiltration in each dialysis session. However, our study did not show any such trend.

Prescription of particular medications maybe due to physician's perceived risk of adverse events, cardiovascular risk factors, availability, and affordability of various drugs. CCBs have been shown to decrease stroke and cardiovascular mortality.<sup>6</sup> They possibly interfere with the process of vascular calcification and attenuate the effect of calcium ions from the dialysate on the vasculature. The effectiveness of CCBs in reducing peripheral vascular resistance and ability to lower BP in volume overload as well<sup>7</sup> has led to their rampant use in dialysis patients. Once-a-day dosing of most of the CCBs also tilts the balance in their favor. Present study also depicts high usage of CCBs.

Angiotensin-converting enzyme (ACE) inhibitors have been shown to decrease residual renal function loss<sup>8</sup> and mortality.<sup>9</sup> Despite evidence pepping in favor of ACE inhibitors/angiotensin receptor blockers in ESRD population, the use of these medications was dismal in our study (► **Table 2**). This stands in sharp contrast to the study by

**Table 3** Doses of antihypertensive agents

	≤12 months (n = 131)	>12 months (n = 119)	p-Value
ACE/ARBs (mg) Telmisartan	50 ± 20	33.3 ± 11.5	0.07
Calcium channel blockers (mg) Amlodipine Cilnidipine Nifedipine (retard) Benidipine	8.393 ± 2.629 16.667 ± 4.923 62.857 ± 26.713 8.00 ± 0.00	7.946 ± 2.864 10.00 ± 0.00 59.524 ± 25.08 00	1.00 0.962 0.965
β-blockers (mg) Carvedilol Metoprolol succinate Atenolol Nebivolol	35.833 ± 13.823 90.625 ± 21.650 100.00 ± 0.00 5 ± 0.00	26.704 ± 15.740 65.441 ± 31.239 25.00 ± 0.00 00	0.544 0.001 0.010
Central α-2 agonist (mg) Clonidine	0.356 ± 0.143	0.400 ± 0.186	0.114
α-blockers (mg) Prazosin (XL)	10.95 ± 5.54	15.00 ± 5.07	0.001
Diuretics (mg) Torsemide Metolazone	51.20 ± 24.690 8.333 ± 2.581	58.57 ± 47.743 0.00	0.372
Direct vasodilators (mg) Minoxidil	00	8.33 ± 2.582	
Aldosterone antagonists Spironolactone	37.5 ± 17.67	00	

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Chang et al, reporting a much higher usage (40%).<sup>10</sup> This is perhaps related to high/-high normal values of serum potassium levels in our study patients (→**Table 1**) and the fear of arrhythmias with hyperkalemia which may go undetected.

The BBs have a proven role in heart failure and coronary artery disease patients.<sup>11</sup> Since deaths in dialysis patients are predominantly attributed to cardiovascular reasons, BBs are usually given priority over other classes of antihypertensive agents. In our study too, they were used in majority of patients (64.8%). In our study, carvedilol was used in much

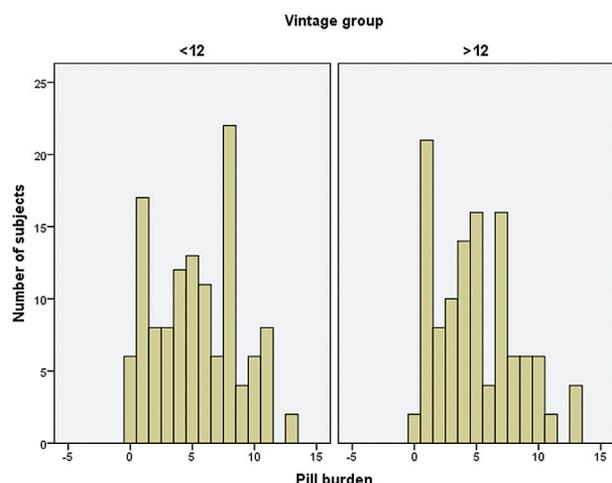
higher percentage as compared with other BBs in >12 months' vintage group. This could possibly stem from the evidence in their favorable effects in dilated cardiomyopathy<sup>12</sup> and better BP control due to lesser removal during dialysis.<sup>13,14</sup>

The α-blockers are used mostly in difficult to control BP in patients on multiple antihypertensive agents.<sup>15</sup> In our study, they were used as third/fourth-line agents and were required in higher doses in later period of dialysis vintage.

Centrally acting sympathetic agents are primarily used in patients with intradialytic hypertension and poorly controlled BP.<sup>15</sup> They have a longer t<sub>1/2</sub> of 18 to 41 hours,<sup>15</sup> reported in dialysis patients. Considering their contribution to the pill burden, a change to less frequent dosing regimen is advisable. Their higher use in this study stands in contrast to the study by Peter et al,<sup>16</sup> showing a much lesser use of approximately 19%. Lower price and physicians' mindset about the perceived efficacy probably have resulted in their wider usage.

Direct vasodilators are the last resort drugs in patients with resistant hypertension. Problem of fluid retention can worsen with these drugs. In our study, its use was seen to be limited to those requiring more than four antihypertensives.

Mineralocorticoid antagonists (MCAs) are sometimes used in difficult to control hypertension. Though there is some data to support its use,<sup>17</sup> risk of hyperkalemia is an inhibitory factor. In our study, it was seen to be used in only two patients and both these were on five antihypertensive medications which puts them in the last resort category in poorly controlled BPs.


**Fig. 1** Pill burden in ≤12 and >12 months' vintage groups.

**Table 4** Antihypertensive pill burden

Antihypertensive pill burden by class	≤12 months (n = 131)	>12 months (n = 119)	p-Value
ACE/ARBs 1	04	03	
Calcium channel blockers 1 2 3 4	73 15 24 01	73 11 23 00	
β-blockers 1 2	35 49	18 52	
Central α-2 agonist 2 3 4	12 62 00	24 46 06	
α-blockers 1 2	12 30	02 34	
Diuretics 1 2	32 18	18 10	
Direct vasodilators 1	00	06	
Aldosterone antagonists 1	02	00	
Mean ± SD	5.4 ± 3.36	5.0 ± 3.25	0.355

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; SD, standard deviation.

Diuretics have been used to control interdialytic weight gain in patients with residual renal function. However, their use drops significantly beyond the first year of dialysis coinciding with the loss of residual renal function.<sup>18</sup> The benefits of using diuretics range from limiting interdialytic weight gain, avoidance of hyperkalemia and reducing incidence of congestive heart failure. Their use in twice a week dialysis regimen is of particular significance in countering the interdialytic weight gain. In our study, we found a significantly lower interdialytic weight gain in patients who were using diuretics ( $2.25 \pm 0.96$  vs.  $2.69 \pm 0.93$  kg;  $p = 0.01$ ). Hyperkalemia was also lower in diuretic users, although not significant. ( $5.05 \pm 0.82$  vs.  $5.44 \pm 2.05$  mEq/L;  $p = 0.055$ ; not shown in table).

Our analysis provides in-depth description of contemporary antihypertensive prescribing pattern. It provides support to the use of diuretics, as long as residual renal function allows, for decreasing interdialytic weight gain and avoidance of hyperkalemia. Wider use of CCBs and BBs is possibly a need of the hour. But there is insufficient data to support the use of a particular type of CCB or BB for which further studies are required.

The pill burden among patients on maintenance dialysis is quite high.<sup>4</sup> This can lead to high treatment cost and non-

compliance to the medications. Drug combinations were less commonly used in our study. Once daily dosing and greater use of drug combinations can help decrease the pill burden and improve compliance too.<sup>19</sup>

The 2D ECHO findings showed high prevalence of concentric left ventricular hypertrophy (72.4%) which is in line with the existing data of 70 to 90%.<sup>20</sup> It was significantly more common in >12 months' vintage group likely related to the severity and duration of hypertension. Functional tricuspid and mitral regurgitations are also common in this population mostly caused by the functional effects of poorly controlled hypertension and volume overload. The same is evident from our study results. Aortic stenosis was rarely reported in our patients (1.6%). This is contrary to the higher reported prevalence of 6 to 13%.<sup>21</sup> No correlation between ECHO findings and use of particular class of antihypertensives was seen in our study. Structural and functional abnormalities revealed by 2D ECHO can help initiate specific antihypertensive therapy to ameliorate the abnormalities. CCBs and ACE inhibitors have been shown to reduce left ventricular hypertrophy and also improve diastolic dysfunction.<sup>22,23</sup> The low use of ACE inhibitors in our study calls for steps to improve the current practice. Measures for better control of serum potassium can certainly help improve this.

## Limitations

Our study has some limitations. Being a single-center study, this antihypertensive prescribing pattern may not reflect patterns in other distant dialysis facilities of this country. Measures for accurate monitoring of volume status, like change in hematocrit and bioimpedance analysis, can throw light on the chronic volume overload status in a subset of patients with poorly controlled BPs. We did not use ambulatory blood pressure monitoring (ABPM) in this study which might have given a better picture of interdialytic BP trend.

## Conclusion

Individualization of antihypertensive therapy, keeping in mind the cardiovascular status, volume control, residual renal function, and susceptibility to potential side effects, is the key to an optimal management of hypertension in dialysis patients. Further research studies should take into account the changes in prescription patterns and influence of these on cardiovascular morbidity and mortality.

### Informed Consent

Informed consent was obtained from all individual participants included in the study.

### Conflict of Interest

None declared.

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