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Effect of amlodipine versus bisoprolol in hypertensive patients on maintenance hemodialysis

A randomized controlled trial

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Abstract

Background: Left ventricular hypertrophy and asymmetric dimethylarginine (ADMA) are surrogate markers of cardiovascular disease (CVD) in the dialysis population. This study aimed to evaluate the effect of a calcium channel blocker-based antihypertensive regimen compared to a beta-blocker-based antihypertensive regimen on left ventricular mass index (LVMI) and ADMA levels in hypertensive patients on hemodialysis (HD).

Methods: This was a parallel-design, open-label, single-center randomized controlled trial on 46 hypertensive patients on maintenance HD, with no history of CVD. Patients were randomly assigned to receive amlodipine 10 mg/d (n = 23) or bisoprolol 10 mg/d (n = 23). Office-based blood pressure (BP) was targeted to ≤ 140/ 90 mm Hg. The outcome was the change in LVMI and ADMA from baseline to 6 months.

Results: Baseline demographic and clinical characteristics did not vary between groups. After 6 months of treatment, amlodipine-based therapy induced a greater reduction in LVMI from baseline than bisoprolol-based treatment (35 ± 34.2 vs 9.8 ± 35.9 gm/m^2; $P = .017$). A similar reduction in the mean BP occurred with treatment in both groups. ADMA concentration decreased significantly from baseline in the amlodipine group (0.75 ± 0.73 to 0.65 ± 0.67 nmol/mL; $P = .001$), but increased nonsignificantly in the bisoprolol group (0.64 ± 0.61 to 0.78 ± 0.64 nmol/mL; $P = .052$).

Conclusion: This study showed that compared to a bisoprolol-based regimen, an amlodipine-based antihypertensive regimen resulted in a significantly greater reduction in LVMI and ADMA levels from baseline in hypertensive patients on HD despite similar BP reduction in both groups. These findings support the re-evaluation of amlodipine as a potential first-line antihypertensive treatment in patients on HD without previous CVD.

Trial Registration: Clinicaltrials.gov Identifier: NCT04085562, registered September 2019.

Abbreviations: β-blockers = beta-blockers, ACEIs = angiotensin-converting enzyme inhibitors, ACS = acute coronary syndrome, ADMA = asymmetric dimethylarginine, ARBs = angiotensin receptor blockers, BP = blood pressure, BSA = body surface area, CCB = calcium channel blocker, CFB = change from baseline, CVD = cardiovascular disease, CVEs = cardiovascular events, DBP = diastolic blood pressure, ESRD = end-stage renal disease, HD = hemodialysis, HF = heart failure, IVSD = interventricular septal thickness at end-diastole, LVEDD = left ventricular end-diastolic dimension, LVH = left ventricular hypertrophy, LVM = left ventricular mass, LVMI = left ventricular mass index, PWD = posterior wall thickness at end-diastole, RCTs = randomized controlled trials, SBP = systolic blood pressure.

Keywords: amlodipine, asymmetric dimethylarginine, bisoprolol, hemodialysis, left ventricular hypertrophy

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1. Introduction

Patients on dialysis have a higher risk of cardiovascular morbidity and mortality than the general population.[1] Hypertension is highly prevalent in the dialysis population and is uncontrolled in most patients.[2] Elevated blood pressure (BP) is one of the risk factors for increased cardiovascular mortality in dialysis patients, particularly when measured outside the dialysis unit.[3,4] Meta-analyses of clinical trials have shown that using pharmacological antihypertensive treatment to lower BP reduces cardiovascular morbidity and mortality in this population.[5,6]

Left ventricular hypertrophy (LVH) is another risk factor associated with cardiovascular mortality that is highly prevalent in the dialysis population.[1] LVH was found to independently predict mortality in dialysis patients.[7,8] The widespread presence of LVH in the dialysis population might be a consequence of inadequate diagnosis and treatment of hypertension.[9] Hypertension is a modifiable risk factor associated with LVH.[10] Antihypertensive therapy and BP control can reduce LVH in dialysis patients and this regression is associated with decreased cardiovascular mortality and improved all-cause survival.[11] Many clinical trials showed that various drug classes, including beta-blockers (β-blockers), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs), can cause regression of LVH in patients on hemodialysis (HD).[12–14] Meta-analyses of randomized controlled trials (RCTs) showed that β-blockers are inferior to other antihypertensive drug classes in causing LVH regression.[15–17]

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase and a uremic toxin that is significantly increased in end-stage renal disease (ESRD). ADMA has been reported to be a solid independent predictor of overall mortality and cardiovascular outcomes in dialysis patients,[18,19] and it was also associated with LVH.[20] One trial showed that ADMA levels were significantly reduced by either amlodipine or valsartan administration in patients on HD.[21]

Both LVH and ADMA are surrogate markers for cardiovascular disease (CVD) in patients on HD; hence, their reduction may be associated with a decreased incidence of CVD. To our knowledge, no study has examined a head-to-head comparison of CCBs and β-blockers in the dialysis population pertaining to surrogate markers of CVD such as LVH.

The aim of this study was to assess the efficacy of an amlodipine-based antihypertensive regimen compared to a bisoprolol-based antihypertensive regimen in reducing left ventricular mass index (LVMI) and serum ADMA levels from baseline in hypertensive patients on HD.

2. Materials and methods

This was an open-label, parallel-group, single-center, randomized controlled trial that compared the efficacy of an amlodipine-based antihypertensive regimen versus a bisoprolol-based antihypertensive regimen with respect to change from baseline (CFB) in LVMI and serum ADMA levels in patients on HD. The study was conducted in accordance with the Declaration of Helsinki (1989), and written informed consent was obtained from all patients. The study protocol was approved by the Research Ethics Committee of the Faculty of Pharmacy, Damanhour University (Reference no: 719PP15) and by the Ethics Committee on Human Research of the Faculty of Medicine, Alexandria University (Reference no: 0201243).

2.1. Participants

All patients attending the HD unit at the Alexandria University dialysis center between September 2019 and June 2020 were screened for eligibility. Eligible patients were approached with informed consent. Patients aged 18 years or older who had ESRD treated with chronic HD three times a week for at least 3 months with hypertension as determined by predialysis BP > 140/90 mm Hg, postdialysis BP > 130/80 mm Hg, home-measured BP, or office-based BP > 140/90 mm Hg and/or on antihypertensive medication, were included. Patients were excluded if they had history of malignancy, history of significant valvular heart disease, chronic congestive heart failure, history of coronary artery disease, ongoing atrial fibrillation, history of myocardial infarction or stroke, history of drug abuse or known contraindication to bisoprolol or amlodipine.

2.2. Study design

2.2.1. Randomization. Forty-six patients were recruited over a period of 10 months and were randomized in a 1:1 ratio to either amlodipine-based therapy or bisoprolol-based therapy using concealed opaque envelopes, using permuted block randomization according to a manually generated random sequence by a technician. Both outcome evaluators and statistical analysts were blinded to the treatment group assignments.

2.3. Baseline period

BP was monitored over the 1-month baseline period with two weekly office visits on the first dialysis day of the week, a predialysis visit, and a postdialysis visit. During the baseline period, no changes to the previous antihypertensive therapy were made. Baseline echocardiography was performed, and blood samples were collected before starting the trial drugs.

2.4. Drug dosing and titration

After the baseline period, the previous antihypertensive regimen was stopped, and patients were subsequently treated with either bisoprolol 10 mg/d or amlodipine 10 mg/d. Doxazocin, alpha-methyldopa, and ACEIs/ARBs were added at a suitable dose and titrated gradually to try to achieve the office-based BP target of ≤ 140/90 mm Hg. Only doxazocin, alpha-methyldopa, and ACEIs/ARBs were available for use in this study. Drug addition, dose evaluation, and dose adjustment were conducted at least monthly. The duration of the study was 6 months.

2.5. Blood pressure measurements

For the duration of the study, office-based BP measures were taken on the first dialysis day of the week in two planned visits, a predialysis visit, and a postdialysis visit. BP was measured using a mercury sphygmomanometer with the patients in a supine position. Prior to BP measurements, the patients rested in the supine position for at least 5 minutes. Measurements were repeated weekly until the end of the study. The average of the four weekly visits was reported as the mean monthly BP. Dry weight was assessed clinically by physical examination and adjusted at baseline.

2.6. Echocardiography

Echocardiography was performed before starting treatment on an interdialytic day before the midweek HD session. Using

M-mode echocardiography, the same examiner performed the recordings at baseline and 6-months. The examiner was blinded to treatment allocation. Left ventricular dimensions and ejection fraction were measured according to the American Society of Echocardiography recommendations.[22] Left ventricular mass (LVM) was calculated using the following equation:

LVM (g) = 0.8 {1.04 [([left ventricular end-diastolic dimension (LVEDD) + Interventricular septal thickness at end-diastole (IVSD) + posterior wall thickness at end-diastole (PWD)]^3 − LVEDD^3)]} + 0.6,

Where LVEDD is the left ventricular end-diastolic dimension (mm), IVSD is the interventricular septal thickness at end-diastole (mm), and PWD is the posterior wall thickness at end-diastole (mm). LVM was indexed using both body surface area and height$^{2.7}$ for the calculation of LVMI. Relative wall thickness was determined using the equation ($2 \times$ PWD/ LVEDD).[22]

2.7. Blood sampling

Blood samples were collected in the morning before the midweek dialysis session for ADMA measurement and routine dialysis unit laboratory investigations. Samples for ADMA measurement were kept on ice for 20 minutes and centrifuged for 20 minutes at 4000 rpm in a normal centrifuge. Serum was separated and stored in a -80°C freezer until analysis using a commercially available enzyme-linked immunosorbent assay kit with a sensitivity of 0.01 nmol/ml.

2.8. Statistical analysis

Descriptive statistics are reported as means and standard deviations. Baseline characteristics and study outcomes were compared between the treatment groups using student *t*-test for normally distributed quantitative variables, Mann-Whitney test for non-normally distributed quantitative variables, and Chi-square test (Fisher or Monte Carlo) for categorical data. The significance of change within each group was analyzed using a paired *t*-test for normally distributed quantitative variables or Wilcoxon signed ranks test for non-normally distributed quantitative variables. All analyses were conducted using IBM SPSS software package version 20 (IBM Corp, Armonk, NY). The significance of the obtained results was judged at a statistical significance level of P-value $< .05$.

3. Results

Between September 2019 and June 2020, 46 patients undergoing regular HD diagnosed with hypertension in Alexandria University's main dialysis center were recruited in this study and randomized into two groups to receive either an amlodipine-based antihypertensive regimen or a bisoprolol-based antihypertensive regimen. The trial flowchart is shown in Figure 1.

3.1. Baseline characteristics and drugs

The baseline demographic and clinical characteristics did not differ significantly between the amlodipine and bisoprolol groups, and the age difference between the two groups did not achieve statistical significance ($P = .131$) (Table 1). All patients were prescribed regular bicarbonate standard dialysis for 4 hours, three times a week using low-flux membrane dialyzers. Owing to safety concerns, no washout period was employed, and only

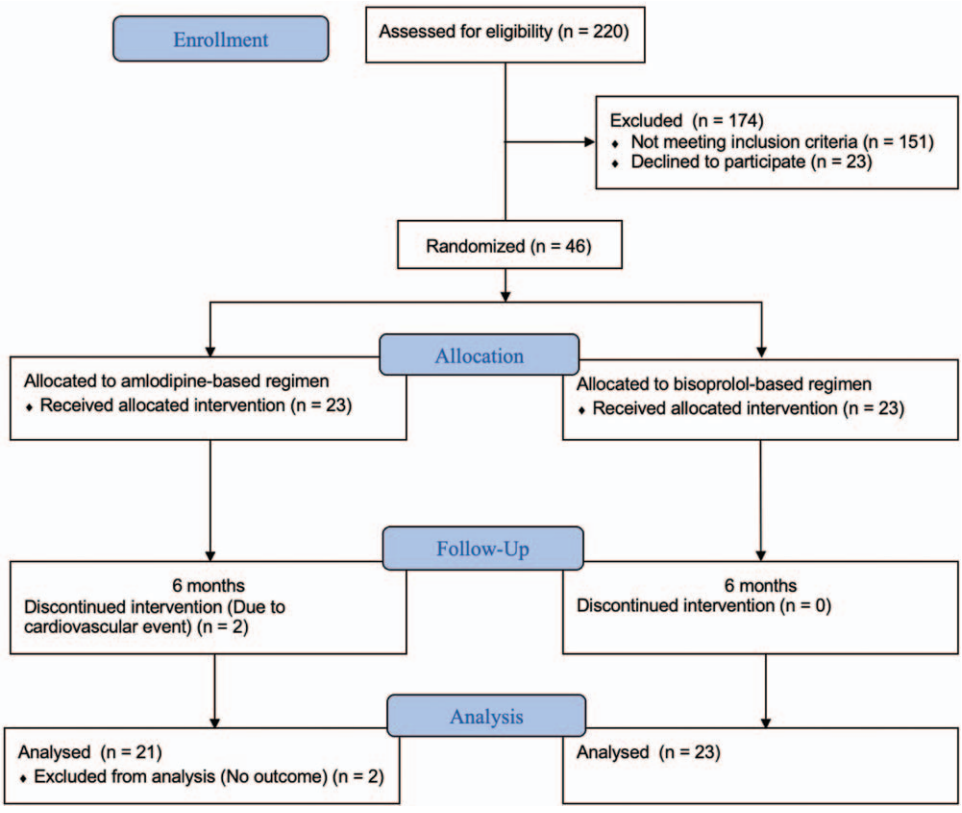

Figure 1. Flowchart of the trial.

Table 1

Baseline characteristics of the study sample.

Clinical characteristic	Amlodipine group (n = 23)	Bisoprolol group (n = 23)	*P*
Age (yr)	43.3 ± 14.1	50.2 ± 16	.131
Gender			
Male	15 (65.2%)	17 (73.9%)	.522
Female	8 (34.8%)	6 (26.1%)	
Access type			
AV fistula	17 (73.9%)	21 (91.3%)	.243
Catheter	6 (26.1%)	2 (8.7%)	
Dialysis duration (mo)	56.7 ± 68.4	69.7 ± 77	.244
Diabetes	3 (13.0%)	2 (8.7%)	1
Smoker			
No	14 (60.9%)	15 (65.2%)	1
Yes	7 (30.4%)	7 (30.4%)	
Former smoker	2 (8.7%)	1 (4.3%)	
Weight (kg)	69.7 ± 16.6	76.5 ± 10.7	.105
Height (cm)	165.6 ± 9.6	168 ± 7.1	.340
Body mass index (kg/m^2)	25.3 ± 4.8	27.2 ± 3.8	.148
Previous transplant	2 (8.7%)	2 (8.7%)	1
Antihypertensive drugs use at baseline			
No antihypertensive drug use, n (%)	2 (8.7%)	6 (26.1%)	.243
Calcium channel blockers, n (%)*	19 (82.6%)	12 (52.7%)	.028*
Alpha-Blockers, n (%)	1 (4.3%)	4 (17.4%)	.346
Centrally acting agents, n (%)	4 (17.4%)	6 (26.1%)	.475
Beta-Blockers, n (%)	10 (43.5%)	12 (52.2%)	.555
RAAS inhibitors, n (%)	3 (13%)	5 (21.7%)	.699
Other drugs use at baseline			
Vitamin D, n (%)	2 (8.7%)	2 (8.7%)	1
Oral Calcium, n (%)	13 (56.5%)	12 (52.2%)	.767
EPO, n (%)	16 (69.6%)	15 (65.2%)	.753
Vitamin B complex, n (%)	21 (91.3%)	20 (87%)	1
Intravenous iron, n (%)	5 (21.7%)	3 (13%)	.699
Insulin, n (%)	3 (13%)	2 (8.7%)	1
Oral hypoglycemic agents, n (%)	1 (4.3%)	0 (0%)	1
Noncalcium phosphate binder, n (%)	2 (8.7%)	0 (0%)	.49
Proton pump inhibitors, n (%)	15 (65.2%)	17 (73.9%)	.522
Aspirin, n (%)	4 (17.4%)	3 (13%)	1

Data are expressed as mean ± standard deviation, or number (%).

EPO = erythropoietin stimulating agents, RAAS = Renin-angiotensin-aldosterone system.

p: *P*-value for comparing between the two studied groups

* $P < .05$ for comparison between the two groups.

previously taken β-blockers were tapered gradually over the last 7 days of the baseline period under close monitoring. Most patients received antihypertensive medications before randomization. The previous treatment was maintained with no modifications during the baseline period. With the exception of CCBs, which were used by a greater number of patients in the amlodipine group, there was no significant difference between the two groups in terms of medications classes used at baseline (Table 1).

Two patients in the amlodipine group did not complete the study due to the incidence of acute coronary syndrome (ACS) (n = 1) or heart failure (HF) (n = 1). The patient who experienced ACS was receiving amlodipine only, whereas the patient who developed HF was receiving amlodipine plus alpha-methyldopa. The incidence of these combined cardiovascular events (CVEs) did not reach statistical significance between the two treatment groups ($P = .489$).

3.2. Laboratory parameters and weight

Laboratory parameters including urea, hemoglobin, creatinine, urea reduction ratio, calcium level, and phosphorus level did not demonstrate a significant difference between treatment groups at baseline or 6-months. Dry weight showed no significant difference at baseline ($P = .078$) and 6-months ($P = .180$) between the two treatment groups, and the average interdialytic weight gain also showed no significant difference between the two groups at baseline ($P = .816$) and 6-month ($P = .741$) (Table 2).

3.3. Blood pressure measurements and control

An average of four pre-dialysis and four post-dialysis office-based BP measurements were reported at baseline and monthly during the study period (Fig. 2). There was no significant difference in BP control between the two study groups at baseline or during any month for the study duration. Both treatments caused a significant reduction in both predialysis and postdialysis office-based BP at 6 months from baseline. At 6 months, both agents significantly decreased diastolic BP (DBP) and systolic BP (SBP) compared with that at baseline ($P < .001$). Decrease in BP from baseline in the amlodipine group compared to the bisoprolol group in predialysis SBP (Fig. 2A) (18.9 ± 10.5 vs 24.5 ± 18.8 mm Hg; $P = .334$), postdialysis SBP (Fig. 2B) (19.1 ± 12.9 vs 18.6 ±

Table 2

Comparison of some biochemical parameters and weight between two study groups at baseline and 6 months.

Parameter	Amlodipine group (n = 22)		Bisoprolol group (n = 23)		P_1	P_2
	Baseline	6 mo	Baseline	6 mo		
Calcium, mg/dL	8.9 ± 0.8	8.8 ± 1	8.8 ± 0.5	9 ± 1.1	.60	.584
Phosphorus, mg/dL	6.2 ± 2	6.2 ± 2.2	5.3 ± 2.1	6.2 ± 2	.169	.946
Hemoglobin, gm/dL	10.1 ± 1.5	10.4 ± 1.6	9.7 ± 1.6	9.8 ± 1.1	.399	.181
Urea, mg/dL	132.1 ± 47	133.6 ± 35.9	148 ± 32	148.5 ± 30.4	.192	.138
Creatinine, mg/dL	9.9 ± 3.1	10.2 ± 2.5	11 ± 2.2	11.5 ± 2.5	.694	.383
URR, %	64.2 ± 10.3	65 ± 8.2	66.4 ± 8.4	64.2 ± 10.4	.159	.079
Interdialytic weight gain (kg)	2.8 ± 1.1	3.1 ± 1	2.9 ± 1.4	3 ± 1.3	.428	.778
Dry weight (kg)	69 ± 16.7	70.7 ± 17.6*	76.5 ± 10.7	76.7 ± 11.3	.078	.180

Data are expressed as mean ± standard deviation.

URR = Urea reduction ratio.

p_1: *P*-value for **Student t-test** for comparing between **Amlodipine** and **Bisoprolol** at **baseline.**

p_2: *P*-value for **Student t-test** for comparing between **Amlodipine** and **Bisoprolol** at **6-months.**

* $P < .05$ for change from baseline.

13.6 mm Hg; $P = .838$), predialysis DBP (Fig. 2C) (10.8 ± 7.5 vs 9.5 ± 9.2 mm Hg; $P = .465$), and postdialysis DBP (Fig. 2D) (11 ± 7.6 vs 7.8 ± 6.3 mm Hg; $P = .216$) showed nonsignificant differences.

There was no statistically significant difference between the two groups in terms of the number of antihypertensive medications received at baseline and during every month throughout the trial (Fig. 3). There was also no significant difference in the number of patients who received ACEIs, ARBs, doxazocin, or alpha-methyldopa between the amlodipine and bisoprolol groups during the course of the trial (Table 3).

3.4. Echocardiographic measurements

Baseline echocardiographic measurements showed no significant differences between the two groups. Table 4 summarizes the echocardiographic data at baseline and 6 months after treatment. After 6 months of treatment, CFB in LVMI was significantly greater in the amlodipine group than in the bisoprolol group, indexed using both body surface area (35 ± 34.2 (95% CI 19.46 – 50.59) vs 9.8 ± 35.9 (95% CI -5.70 – 25.35) gm/m^2; $P = .017$) and height$^{2.7}$ (14.5 ± 15.4 (95% CI 7.50 – 21.49) vs 4.1 ± 17 (95% CI -3.25 – 11.44) gm/m$^{2.7}$; $P = .03$) (Fig. 4). LVM was also significantly lower in the amlodipine group than in the bisoprolol

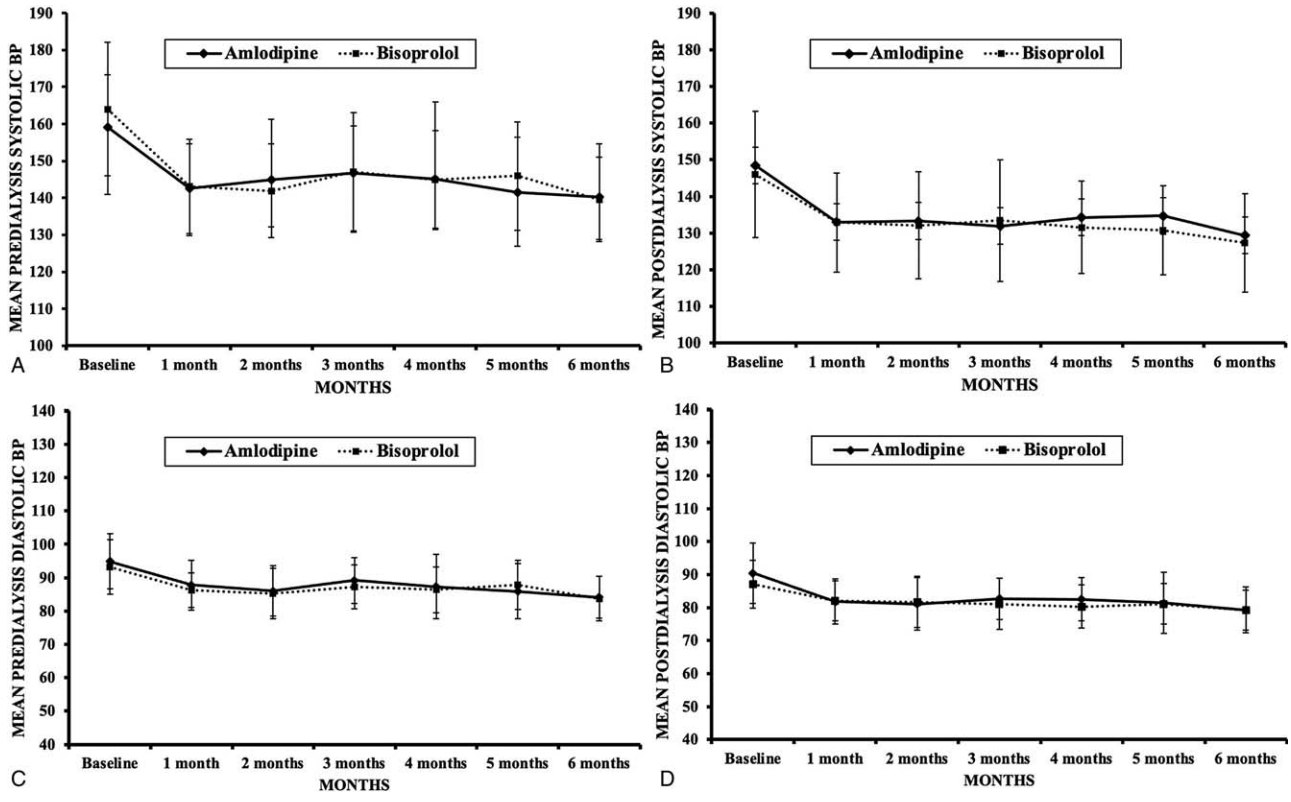

Figure 2. Comparison between the two treatments according to predialysis office-based systolic blood pressure (SBP) (A), postdialysis office-based SBP (B), predialysis office-based diastolic blood pressure (DBP) (C), and postdialysis office-based DBP (D). No significant differences in BP control were observed between the two groups at any stage.

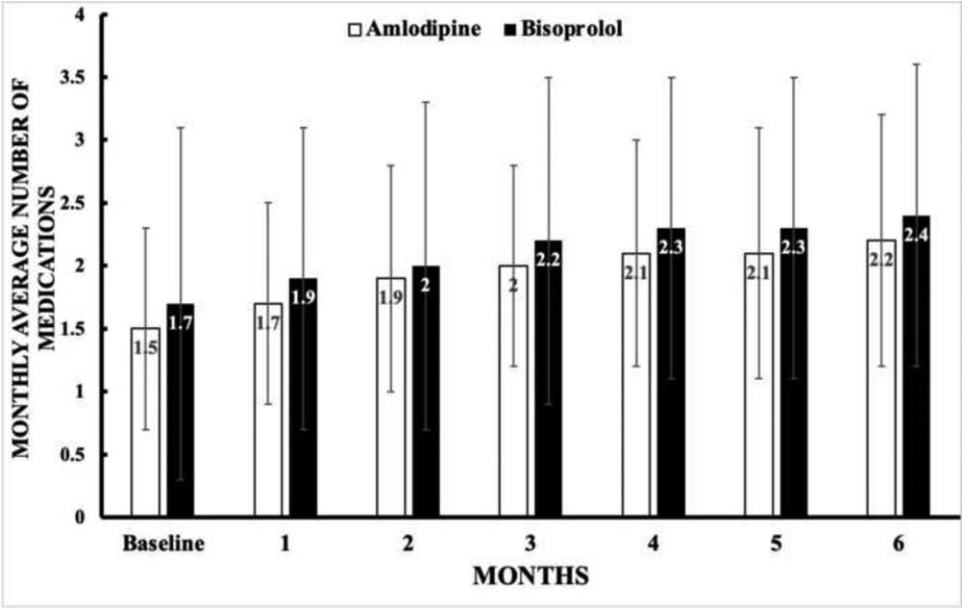

Figure 3. The number of average monthly antihypertensive medications. No significant difference was found between the two groups at any stage of the trial.

Table 3

Type and number of other antihypertensive drugs received during the trial.

Drug	Amlodipine group (n = 23)	Bisoprolol group (n = 23)	*P*
ACEI, n (%)	3 (13%)	6 (26.1%)	.459
ARBS, n (%)	3 (13%)	3 (13%)	1
Doxazocin, n (%)	15 (65.2%)	15 (65.2%)	1
Alpha-methyldopa, n (%)	5 (21.7%)	8 (34.7%)	.326

Data are expressed as number (%).
ACEIs = angiotensin-converting enzyme inhibitors, ARBs = angiotensin receptor blockers.
p: *P*-value for comparing between the two studied groups.

group (227.9 ± 57.1 vs 276.7 ± 65.4 gm; $P = .012$). There was a significant difference in the IVSD (P value = 0.018) after 6 months between the two groups, suggesting that a higher reduction in IVSD in the amlodipine group was the main cause of the significant difference in LVMI regression.

3.5. Serum ADMA level

ADMA serum concentrations did not differ significantly at baseline between the two groups (P value = .364). ADMA levels significantly decreased from baseline only in the amlodipine group (0.75 ± 0.73 to 0.65 ± 0.67 nmol/mL; $P = .001$), and it increased nonsignificantly from baseline in the bisoprolol group

Table 4

Echocardiographic findings at baseline and 6-months.

	Amlodipine group (n = 21)		Bisoprolol group (n = 23)			
	Baseline	6 mo	Baseline	Post	P_1	P_2
LVEDD, mm	49.2 ± 6.8	50.6 ± 6.2	50.5 ± 7.1	52.3 ± 4.8	.566	.298
LVESD, mm	31.7 ± 8.6	30.5 ± 10.4	33.1 ± 6.4	33.6 ± 4.6	.530	.204
IVSD, mm	14.2 ± 4.2	11.3 ± 3.2	15 ± 2.5	13.4 ± 2.4	.427	.018*
PWD, mm	13 ± 1.7	11 ± 1.8	12.5 ± 2.2	12.1 ± 2.3	.415	.092
EF, %	0.6 ± 0.1	0.7 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	.857	.953
RWT	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	.394	.407
LVM, gm	287.3 ± 76.3	227.9 ± 57.1	295.1 ± 90.2	276.7 ± 65.4	.759	.012*
LVMI, gm/m$^{2.7}$	73.9 ± 18.4	59.4 ± 16.8	72.1 ± 19.7	68 ± 14.2	.756	.073
Decrease from baseline	14.5 ± 15.4		4.1 ± 17			
P_0	< **.001***		**.260**			
LVMI, gm/m^2	161.8 ± 42.5	126.7 ± 36.2	154.9 ± 46.6	145.1 ± 33.3	.615	.087
Decrease from baseline	35 ± 34.2		9.8 ± 35.9			
P_0	< **.001***		**.203**			

Data are expressed as mean ± standard deviation.
IVSD = interventricular septal thickness at end-diastole, LVEDD = left ventricular end-diastolic dimension, LVM = left ventricular mass, LVMI = left ventricular mass index, PWD = posterior wall thickness at end-diastole, RWT = relative wall thickness.
P_0: *P*-value for **Paired t-test** for comparing between **baseline** and **6-months.**
P_1: *P*-value for **Student t-test** for comparing between **Amlodipine** and **Bisoprolol** at **baseline.**
P_2: *P*-value for **Student t-test** for comparing between **Amlodipine** and **Bisoprolol** at **6-months.**
* Statistically significant at $P \leq .05$.

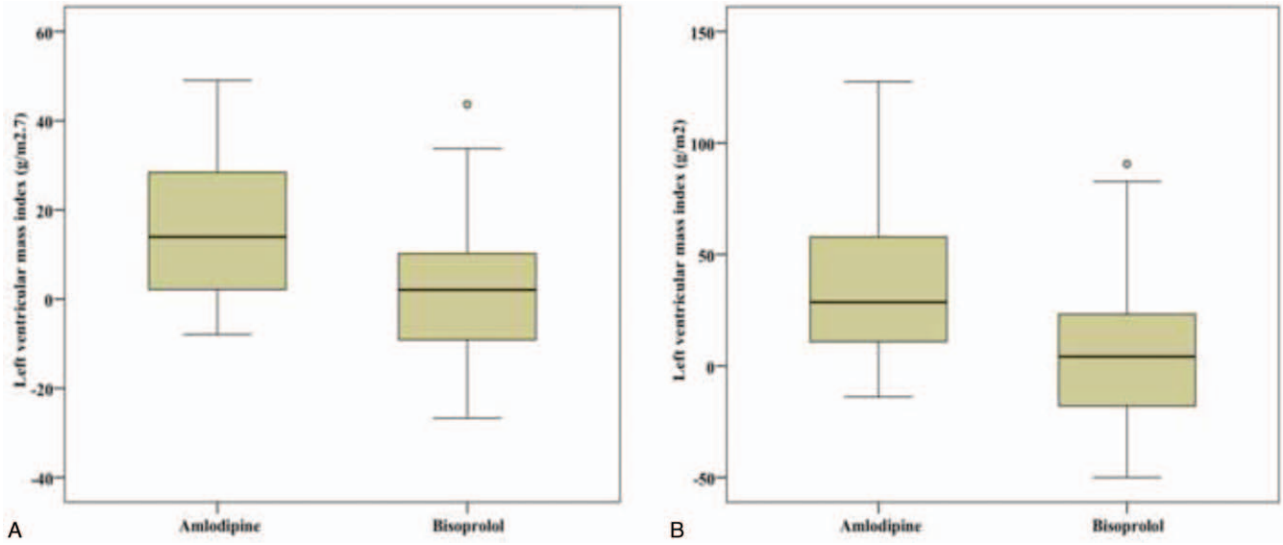

Figure 4. Comparison of change from baseline in the left ventricular mass index indexed using height$^{2.7}$ (A) and body surface area (BSA) (B) between the two groups. The change was significantly higher in the amlodipine group compared to the bisoprolol group using both BSA (35 ± 34.2 vs 9.8 ± 35.9 gm/m^2; $P = .017$) and height$^{2.7}$ (14.5 ± 15.4 vs 4.1 ± 17 gm/m$^{2.7}$; $P = .03$).

(0.64 ± 0.61 to 0.78 ± 0.64 nmol/mL; $P = .052$). CFB was significantly higher in the amlodipine group compared to the bisoprolol group (-0.10 ± 0.19 nmol/mL (95% CI -0.18 – -0.02) vs 0.14 ± 0.44 nmol/mL (95% CI -0.05 – 0.33); $P = .001$) which is equivalent to percentage CFB of (-12.1% ± 14.6% (95% CI -18.59 – -5.68) vs 57.8% ± 155.9% (95% CI -9.67 – 125.2); $P = .001$).

4. Discussion

LVH is an important risk factor for developing CVD. LVH regression and prevention of its advancement or development may be an important target in hypertensive ESRD patients.[23] This study showed that as compared to a bisoprolol-based antihypertensive regimen, therapy with an amlodipine-based antihypertensive regimen effectively induces significantly greater LVMI regression and a greater reduction in ADMA from baseline in hypertensive patients on maintenance HD. There was no significant difference in BP control between the two groups at baseline or during the study period. Both treatment regimens significantly lowered BP from baseline after 6 months.

Few experimental studies have investigated the role of CCBs and β-blockers in the dialysis population. CCBs were found to effectively control BP even in the volume expanded state.[24] Amlodipine was found to reduce a composite endpoint of all-cause mortality, CVEs, stroke, and peripheral arterial disease in dialysis patients in one placebo-controlled RCT by almost 50%.[25] Evidence from these limited reports suggests that CCBs may be effective in providing BP control and prevention of CVD in dialysis patients.

Conversely, a study showed that amlodipine and enalapril caused similar nonsignificant LVMI regression whereas losartan caused significant LVMI regression.[13] Similarly, perindopril significantly reduced LVMI compared to nitrendipine independent of the BP-lowering influence.[26] In one study by Yilmaz et al amlodipine induced regression in LVMI of −9.8% (95% CI, −23.3% to 3.6%) in the subset of the amlodipine group with concentric LVH only, with no significant difference from ramipril, while both drugs caused progression of LVH in patients with eccentric LVH. This study excluded patients who could not achieve a BP target of less than 135/85 mm Hg on maximal dosing of the two agents from the trial.[14] Our sample showed an average relative wall thickness of 0.5, indicating concentric LVH, but individuals were not excluded based on BP target; instead, other antihypertensive medications were added to attain the BP target. There was no imbalance between the two groups regarding the number or type of add-on antihypertensive medications (Table 3).

β-blockers were studied in the dialysis population in two RCTs. One placebo-controlled RCT showed that carvedilol reduced CVD and mortality in dialysis patients with dilated cardiomyopathy, suggesting the value of β-blockers in dialysis patients with HF. It is worth noting that the BP of the treatment arm was lower than that of the placebo group and may have contributed to the observed effect.[27] In another study, a comparison of atenolol and lisinopril for hypertension therapy in HD patients revealed that atenolol may more effectively reduce CVEs than lisinopril while having equal effects on LVMI regression. Significantly better BP control was achieved in the atenolol group, which may have contributed to the difference between the two groups. The previous study's sample was primarily composed of African-American patients. As a result, the validity of extrapolating the results to the overall dialysis population is uncertain.[12] These studies have led to a recommendation for the use of β-blockers as first-line agents in hypertensive patients on HD, especially in patients with HF.

In our study, patients with a history of CVD were excluded, and there was no significant difference in average monthly office-based BP between the two groups at any stage during the trial. Therefore, we can safely attribute the difference in outcome between the two groups to the CCB and β-blocker effects independent of BP control.

There are a limited number of trials on HD patients. The difficulty in recruiting dialysis patients for clinical trials was highlighted in the β-blocker to Lower Cardiovascular Dialysis Events (BLOCADE) trial, which was a feasibility trial designed to establish the tolerance of 6.25 mg carvedilol twice daily in dialysis patients. Only 49 individuals were randomly assigned to receive either carvedilol or placebo after a 21-month recruitment phase at 11 sites. Ten of the 26 carvedilol group participants and four of the 23 placebo group participants dropped out of the trial.[28]

Although no studies have been conducted to compare the usage of CCBs and β-blockers in the dialysis population, the findings of our study may be explained using data from the general population. Meta-analyses of RCTs showed that β-blockers are inferior to CCBs in inducing LVH regression.[15–17] According to one classical study, LVMI regression with nifedipine or perindopril resulted in a similar significant regression of LVMI with similar BP control and this effect may be independent of dosage and extent of BP reduction.[29] This also agrees with results from renal transplant patients where nitrendipine was able to prevent the development of LVH compared to placebo despite similar BP control.[30] This suggests that CCBs may have a BP independent effect on LVH. The underlying mechanism of this action might be explained partly by the growth-stimulating effects caused by intracellular calcium buildup.[31,32] The inferiority of β-blockers in causing LVH regression may be partly explained by the downregulation of adrenergic receptors on the heart in hypertensive patients in response to sympathetic activity, which also limits the efficacy of β-blockers.[33] Another explanation is that β-blockers have an insufficient impact on BP in the central aorta which is a solid predictor of LVH.[34]

In one RCT, the amlodipine-based regimen provided more protection against CVD, with a lower frequency of induced diabetes, compared to the atenolol-based regimen.[35] Although results from the general population cannot be casually extended to the dialysis population, our results suggest that the beneficial role of CCBs in causing higher regression of LVH and thus, preventing CVD, may be extrapolated to the dialysis population.

Elevated ADMA levels appear to be associated with increased CVD and mortality in the HD population.[18,17] Reducing ADMA levels may be converted to a decrease in CVD risk. However, the clinical benefit of lowering ADMA has not yet been confirmed in clinical trials. One study by Aslam et al examined the effect of antihypertensive treatment with valsartan and amlodipine on oxidative stress markers, including ADMA, in patients on dialysis. Both treatments significantly reduced ADMA levels.[21] Our results also demonstrated that amlodipine was able to significantly reduce serum ADMA levels from baseline in the dialysis population. Our reported ADMA levels differed from those reported by Aslam et al. A possible reason is that no washout period could be conducted because of safety concerns. It is quite possible that ADMA levels may be affected by previous medication, as most of our patients were receiving previous antihypertensive treatment that included CCBs and ACEIs/ARBs. Nevertheless, according to a systematic review, ADMA levels in control groups ranged from 0.30 to 1.41 micromol/L, and in dialysis patients, ADMA levels were between 0.59 and 6.0 micromol/L,[36] a range within which our reported average value lies.

Bisoprolol showed a nonsignificant increase from baseline in serum ADMA levels. A previous study also reported no change in ADMA levels on bisoprolol treatment in the general hypertensive population.[37] Another study in the general population showed that ADMA may even increase with metoprolol, a cardioselective β1 receptor blocker similar to bisoprolol. The increase in ADMA was explained by the possible role of β1 receptor antagonists in the production or metabolism of ADMA.[38] ADMA levels appear to increase with selective β1 receptor antagonists. Our results showed a similar trend but without reaching statistical significance. This may suggest a limited role of β1 receptor antagonists in reducing endothelial dysfunction in patients on HD.

To our knowledge, this is the first study to compare CCBs to β-blockers in the dialysis population with respect to the surrogate markers of CVD. This study provides important insights into the role of CCBs in the management of hypertension and prevention of CVD in patients on HD without a history of CVD. As a result, to reduce cardiovascular morbidity and mortality, it is suggested that the role of CCBs in therapy and their potential use as first-line antihypertensive agents in this specific population should be reconsidered.

This study has several limitations, including limited sample size due to the exclusion of all patients with a history of CVD and the single-center nature of the study, an open-label design due to lack of resources for a double-blind study, absence of washout period due to safety concerns, and the inability to use ambulatory BP monitoring due to financial and logistical issues.

5. Conclusion

This study showed that, compared with bisoprolol, amlodipine induced a significantly greater reduction in LVMI and ADMA levels from baseline among hypertensive patients on HD despite similar BP reduction in the two groups. LVH is an independent strong predictor of CVD, and ADMA is a potential surrogate marker of CVD and endothelial dysfunction. Their reduction may be translated into a reduction in CVD in this population. This suggests a stronger role of CCBs, especially amlodipine, in the management of BP in the dialysis population to reduce the risk of CVD and mortality in this population. It is useful to note that this trial excluded patients with a history of CVD. In conclusion, among hypertensive patients on HD with no history of CVD, amlodipine should be reconsidered as a potential first-line antihypertensive agent. Larger multicenter clinical trials should be conducted to confirm these results.

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