Cardiology Research and Cardiovascular Medicine
Desai N, et al. Cardiolog Res Cardiovasc Med 10: 278.
www.doi.org/10.29011/2575-7083.100278
www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Research Article

A Comparative Analysis (TIME-AIM Study) of Achieving Target Blood Pressure Goal in Hypertension Through Initial Dual Combination Therapy and Home Blood Pressure Monitoring

Nagraj Desai[1], Nagamallesh UM[2], Harsha MM[3], Purushottam R[4], Sunil Kumar[5], Arpith MN[6], Prashant Agrawal[7], Jyoti Rana[8*]

[1]Fortis Hospital, Namana clinic Off 4A, New BEL Rd, Seenappa Layout, Jaladarsini Layout, R.M.V. 2nd Stage, Bengaluru, Karnataka 560094, India

[2]Aster CMI, No 43/2 New Airport Road NH 7 Sahakar Nagar Outer Ring Road Bangalore -560092, India

[3]Jaydeva Mysore, Associate Professor Jayadeva Hospital Krs Road Mysore - 570016, India

[4]A J Hospital Manglore, Aj Hospital & Research Centre , Nh 66 , Kuntikana Mangalore, Karnataka 575004, India

[5]JSS Mysuru, Professor And Hod Department of Cardiology Jss Hospital Mysore - 570004, India

[6]Consultant Physician Maruthi Speciality Clinic # 21, 1 st cross gayathri puram main road 2 nd stage udayagiri mysore - 570019, India

[7]Deputy General Manager (DGM) Medical Affairs, Mankind Pharma Ltd., 84, Okhla Industrial Estate Phase III, New Delhi, India

[8]Medical Advisor I Medical Affairs, Mankind Pharma Ltd., 84, Okhla Industrial Estate Phase III, New Delhi, India

***Corresponding author:** Jyoti Rana, Medical Advisor I Medical Affairs, Mankind Pharma Ltd., 84, Okhla Industrial Estate Phase III, New Delhi, India

Citation: Desai N, Nagamallesh UM, Harsha MM, Purushottam R, Kumar S, et al. (2025) A Comparative Analysis (TIME-AIM Study) of Achieving Target Blood Pressure Goal in Hypertension Through Initial Dual Combination Therapy and Home Blood Pressure Monitoring. Cardiol Res Cardio vasc Med 10: 278. DOI: https://doi.org/10.29011/2575-7083.100278

Received Date: 17 March, 2025; **Accepted Date:** 25 March, 2025; **Published Date:** 27 March, 2025

Citation: Desai N, Nagamallesh UM, Harsha MM, Purushottam R, Kumar S, et al. (2025) A Comparative Analysis (TIME-AIM Study) of Achieving Target Blood Pressure Goal in Hypertension Through Initial Dual Combination Therapy and Home Blood Pressure Monitoring. Cardiol Res Cardio vasc Med 10: 278. DOI: https://doi.org/10.29011/2575-7083.100278

Abstract

Objective: We aimed to evaluate and compare the effectiveness, and safety of the dual combination of olmesartan with amlodipine, and with chlorthalidone, along with home BP monitoring (HBPM) and its effect on the quality of life (QoL) in achieving the target blood pressure (BP) in hypertensive Indians. **Method:** It was an investigator-initiated, prospective, open-label, randomized, comparative study; that was conducted across 16 centers in India. Adult patients with uncontrolled BP receiving monotherapy, and/or newly diagnosed stage 2 de novo hypertension, were enrolled and randomized into one of the three treatment groups, (1) Olmesartan medoxomil 20mg + Amlodipine 5mg with HBPM (N=50). (2) Olmesartan medoxomil 20mg + Chlorthalidone (CTLD) 6.25mg with HBPM (N=45). (3) Standard of Care Treatment as per investigator's discretion without HBPM (N=38). **Result:** A total of 133 subjects consisting of 70 (53.3%) males, with a mean age of 53.11 ± 13.17 years completed the study. Mean reductions in sitting SBP/DBP (mmHg) of the subjects on Olmesartan/Amlodipine, Olmesartan/CTLD, and standard of care arm were as follows, day-30 [18.06/10.06, 11.13/8.71, 6.08/4.68], day-60 [19.90/12.08, 13.36/8.96, 8.05/5.29], day-90 [22.22/13, 14.73/10.20, 11.39/5.79], respectively. All three study arms showed a statistically significant reduction in BP from baseline to day-90. The QoL assessment did not report any difference in the groups and subjects with HBPM were satisfied. **Conclusion:** TIMES-AIM demonstrated that the initiation of combination therapy with Olmesartan/Amlodipine (20/5mg) and Olmesartan/CTLD (20/6.25mg), in a single pill, is effective and safe in significantly reducing SBP/DBP in Indian hypertensive patients in the real-world setup with good acceptability for HBPM. Trial Registration no. CTRI/2022/08/045166.

Keywords: Hypertension, combination therapy, Olmesartan, amlodipine, chlorthalidone, HBPM

List of Abbreviations: ARB: Angiotensin receptor blockers; BP: Blood pressure; CCB: Calcium channel blockers; CTLD: Chlorthalidone; DBP: Diastolic blood pressure; DM: Diabetes mellitus; HBPM: Home BP monitoring; FDC: Fixed dose combination; SBP: Systolic blood pressure; SPC: Single-pill combination; QoL: Quality of life

Introduction

Hypertension is considered one of the major modifiable cardiovascular risk factors and affects more than 30% of the adult population worldwide. Its prevalence in Indian adults is 29.8% (urban 33.8%, rural 27.6%) [1]. Hypertension control has been shown to reduce cardiovascular, cerebrovascular, renal diseases, and dementia [1].

Clinical practice guidelines for the management of hypertension recommend efficient screening, diagnosis, monitoring, and management of subjects to reduce the high blood pressure (BP) mediated target organ damage and risks associated with uncontrolled hypertension. Further, emphasis has been placed on out-of-office BP monitoring, especially home BP monitoring (HBPM).

Several hypertension guidelines including the 2023 ESH arterial hypertension management guidelines [2], 2020 International Society of Hypertension Global Hypertension Practice Guidelines' [3], WHO [4] and ICMR [1] recommended that for optimal results, initial combination therapy with two anti-hypertensive agents in a single-pill combination (SPC) is more beneficial than a long-standing concept of starting treatment with a single agent [1,4]. Antihypertensive medications used in combination therapy should be chosen from the three drug classes: diuretics (thiazide or thiazide-like), angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers (ARBs), and long-acting dihydropyridine calcium channel blockers (CCBs) [5]. These guidelines recommend SPC and HBPM for better treatment adherence. A review by An J et al observed that initiating a low-to-standard dose dual-therapy fixed-dose combinations (FDCs) showed better BP control than initiating treatment with a standard-dose monotherapy along with increased medication adherence, reduced clinical inertia, decreased time to BP control, and improved cardiovascular outcomes [6]. Presently, no clinical study data are available on the effectiveness of anti-hypertensive combination therapy and use of guideline-recommended HBPM in the Indian population.

The objective of our study was to evaluate and compare the effectiveness, and safety of the dual combination of olmesartan an ARB with amlodipine a CCB, and olmesartan with chlorthalidone (CTLD) a thiazide-like diuretic, use of HBPM and its effect on the quality of life (QoL) in achieving the target BP in hypertensive Indian patients.

Method and Methodology

It was an investigator-initiated, prospective, open-label, randomized, multicenter, comparative study. The study was conducted at 16 physicians' office practices in India from 1st Dec 2022 to 1st May 2023. A total of 150 subjects who fulfilled the study eligibility criteria were enrolled after explaining the study in detail and receiving voluntary informed consent for study participation.

The inclusion criteria were, patients of either sex, aged ≥ 18 to ≤ 85 years; with uncontrolled BP receiving monotherapy (SBP>140 & DBP>90 mmHg); and/or treatment naïve patients diagnosed with stage 2 de novo hypertension as per ESC/ESH 2018 guidelines on hypertension management; patients prescribed with combination therapy as part of routine clinical practice by the study investigator; and patients who were willing to follow clinical study instructions and complete the patient diaries allotted to them.

Exclusion criteria were, pregnant or breastfeeding women; patients with known liver or kidney dysfunction; patients consuming Ayurvedic/Herbal medicines for hypertension management; patients with suspected or known intolerance to any of the drugs prescribed as combination therapy; presence of any other clinically significant disease or laboratory findings that in the Investigator's opinion may affect the study outcomes or continued participation of the patient in the study; and participation in another study concurrently or within 4 weeks before the Screening Visit.

The primary objective was to evaluate the effectiveness, and the secondary objective was to assess the safety, and QoL (Likert scale) of dual combination therapy in reaching the target BP in hypertensive patients with HBPM when compared to the current standard of care without HBPM.

After receiving voluntary informed consent, the subjects underwent screening procedures [physical examination, medical history, laboratory, and diagnostic investigations (ECG, serum creatinine, serum sodium, serum potassium, HbA1c, FPG, PPG, cholesterol, microalbuminuria, urine examination)]. The eligible subjects were randomized into three treatment groups per the computer-generated randomization schedule (1:1:1). The treatment groups were,

Group 1	Olmesartan medoxomil 20mg + Amlodipine 5mg with HBPM Olmesartan medoxomil 20mg + Amlodipine 10mg with HBPM
Group 2	Olmesartan medoxomil 20mg + CTLD 6.25mg with HBPM Olmesartan medoxomil 20mg + CTLD 12.5mg with HBPM
Group 3	Standard of Care Treatment as per investigator's discretion without HBPM

Patients in group 1 and 2 were provided with respective medications for 30 days along with an HBPM device (OMRON HEM 7156 AAP), and a patient diary. Each subject was trained in recording the BP in a standardized manner in a sitting position. The patients were asked to record morning and evening BP measurements with at least two BP readings each time for 3 consecutive days (day-2,3,4) after every follow-up visit in the provided diary. On study enrollment clinical, biochemical evaluations (Blood investigations and ECG) were done, which were repeated at the final visit. The subjects were required to visit the study investigators' clinic to evaluate the study outcomes every 15 days for 3 months i.e., day- 15, 30, 45, 60,75, and 90, scheduled as visit-1, 2, 3, 4, 5, 6, respectively. The initial target BP was pegged at 140/90 mmHg followed by 130/80 mmHg. Study subjects who did not achieve target BP after 8 weeks of treatment were considered for increasing the dose of FDC per the clinicians' judgment. A telephonic follow-up was performed on the 15th, 45th, and 75th day to ensure patient compliance.

All patients received counseling regarding lifestyle changes including sodium restriction.

Compliance with Ethics Guidelines

All ethical approvals required for the study were obtained before the start of the trial and details have been mentioned in Trial Registration: www.ctri.nic.in. (CTRI/2022/08/045166). The study was approved by the independent ethics committee of Gurushree High Tech multi-specialty hospital, Bengaluru on 15 June 2022. All procedures were followed per the responsible committee on human experimentation and the Helsinki Declaration of 1975 and subsequent revisions.

Statistical Analysis

Continuous data like age, weight, etc. were summarized with n, mean, SD, and range. Categorical data like sex etc. were depicted with count (%). For continuous variables such as SBP, DBP, and HbA1c, mean change from baseline was derived and a paired t-test was applied to assess the statistical significance. For categorical variables such as the percentage of patients achieving target BP, QoL measurement, treatment compliance, and incidence of adverse events, the results were summarized with count (%). Wherever applicable, a chi-square test was performed to assess the statistical significance. Physical examination, vital signs, and changes from baseline were summarized using descriptive statistics. A p-value of <0.05 was considered statistically significant. All the statistical analyses were performed using STATA software.

Results

A total of 150 subjects were enrolled and randomized into the study. The CONSORT flow chart detailing the study enrolment is presented in (Figure 1). Of these, 133 patients completed the study and were included in the final analysis.

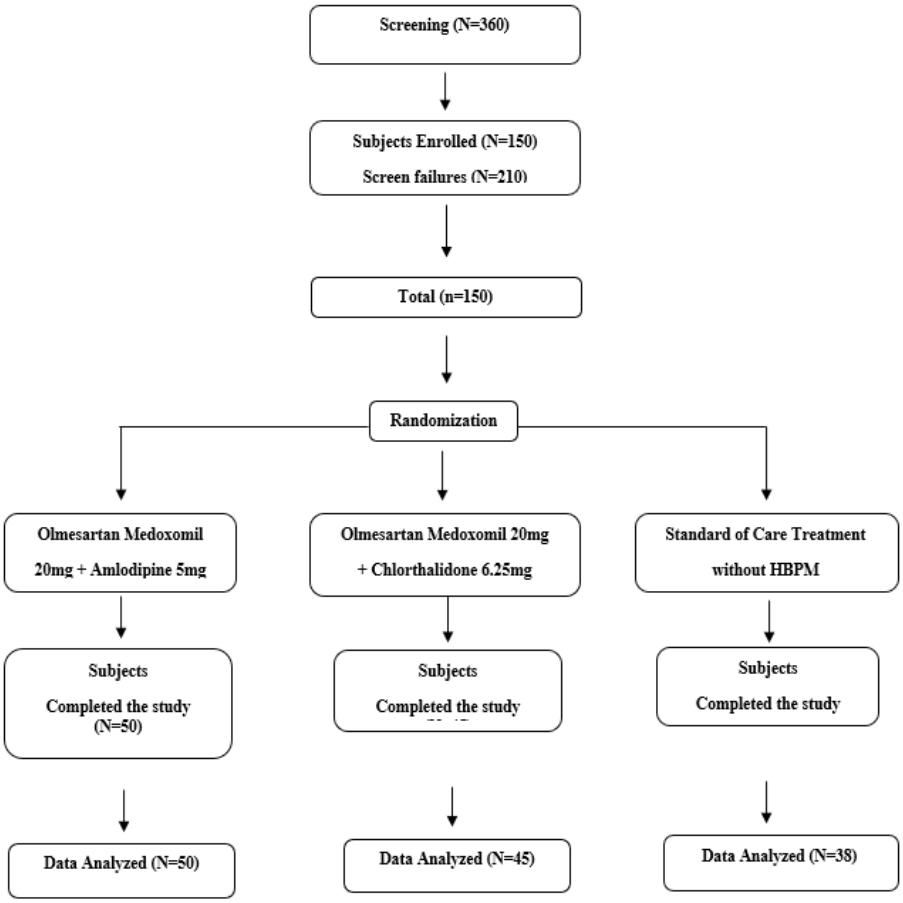


Figure 1: CONSORT flow chart.

Of the total 133 subjects, 70 (53.3%) were men. The mean age of the total study population was 53.11 ± 13.17 years. Study population demographics are presented in (Table 1). Of these 133 subjects, 50 received Olmesartan Medoxomil 20mg + Amlodipine 5mg (Group 1), 45 received Olmesartan Medoxomil 20mg + CTLD 6.25mg (Group 2), With HBPM, and 38 received standard-of-care treatment without HBPM (Group 3). Details of comorbidities are provided in (Table 1). Diabetes mellitus (DM) was present in 56 (42.10%) subjects.

Parameters	**Overall (N=133)**	**Group 1 (N=50)**	**Group 2 (N=45)**	**Group 3 (N=38)**
Age (Years)				
N	133	50	45	38
Mean	53.11 ± 13.17	50.12 ± 12.68	55.11 ± 14.09	54.66 ± 12.28
Age (Groupwise)				
31 - 40	25(18.79 %)	13(26.00 %)	8(17.78 %)	4 (10.52 %)
41 – 50	34(25.56 %)	14(28.00 %)	8 (17.78 %)	12(31.57 %)
51 – 60	35(26.31 %)	14(28.00 %)	13(28.89 %)	8 (21.05 %)
>60	39(29.32 %)	9(18.00 %)	16(35.56 %)	14(36.84 %)

Gender, n (%)				
Male	70(53.03 %)	27(54.00 %)	23(52.27 %)	20(52.63 %)
Female	62(46.96 %)	23 (46.00 %)	21(47.72 %)	18(47.36 %)
Height (Cm)				
N	122	45	41	36
Mean	164.88 ± 8.35	165.60 ± 8.70	164.26 ± 8.62	164.69 ± 7.72
Weight (Kgs.)				
N	124	47	41	36
Mean	71.93 ± 11.46	69.58 ± 11.48	72.01 ± 11.59	74.91 ± 10.88
BMI (Kg/m^2)				
N	121	45	41	35
Mean	26.29 ± 3.63	25.04 ± 3.27	26.66 ± 3.81	27.47 ± 3.44
Concomitant medical history				
Diabetes Mellitus	56(42.10 %)	21(77.78 %)	12(63.15 %)	23(82.14 %)
Dyslipidemia	4(5.40 %)	0 (0.00 %)	3(15.78 %)	1 (3.57 %)
Hypothyroidism	7(9.45 %)	4(14.81 %)	0 (0.00 %)	3 (10.71 %)
Old CVA	1 (1.35 %)	0 (0.00 %)	1 (5.26 %)	0 (0.00 %)
Rheumatoid Arthritis	2(2.70 %)	1(3.70 %)	1 (5.26 %)	0 (0.00 %)
Discectomy	2(2.70 %)	1 (3.70 %)	0 (0.00 %)	1 (3.57 %)
Hypertension	2(2.70 %)	0 (0.00 %)	2(10.52 %)	0 (0.00 %)

Table 1: Summary of subject demographics and comorbidities

Target BP achievement

One of the efficacy parameters recorded for this clinical study was achieving target BP for all patients at the final visit. At Day-90, a target BP of 140/90 mmHg (sitting) was achieved by 80%, 77.78%, and 55.26% of the patients; while BP of 130/80 mmHg was attained by 16%, 11%, and 4% of the subjects from groups 1, 2, and 3, respectively. A summary of the % of subjects achieving target BP (sitting) at each visit is presented in (Figure 2).

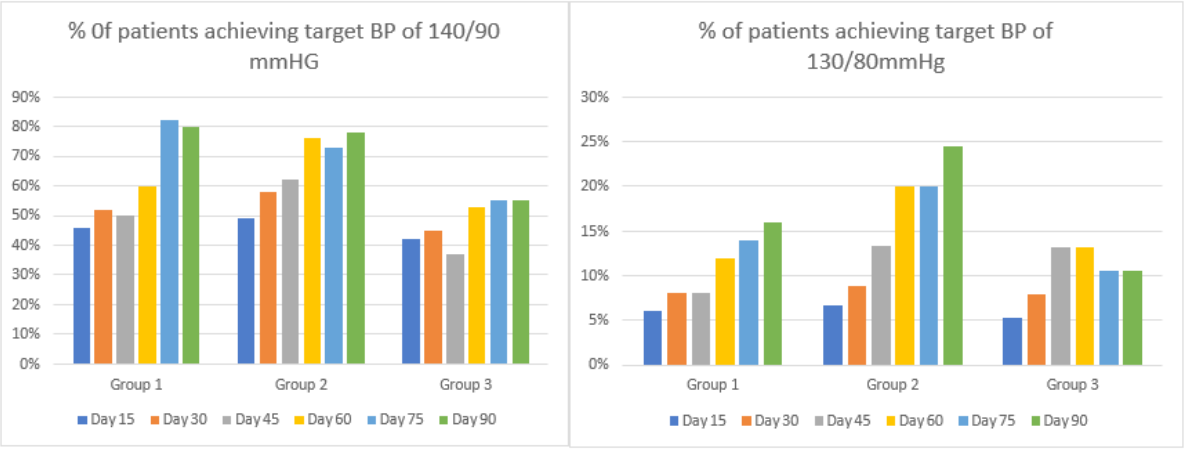


Figure 2: Summary of % Patients achieving target BP of 140/90, and 130/80 mmHg per visit

All three groups reported a statistically significant reduction (p-value across all three groups < 0.0001) in SBP/DBP at the final visit from the baseline. Reductions in mean SBP/DBP at day-90 and heart rate are depicted in (Figure 3). Details of the reduction in average SBP/DBP from baseline to final visit (day-90) in standing position are provided in (Supplement Table 1).

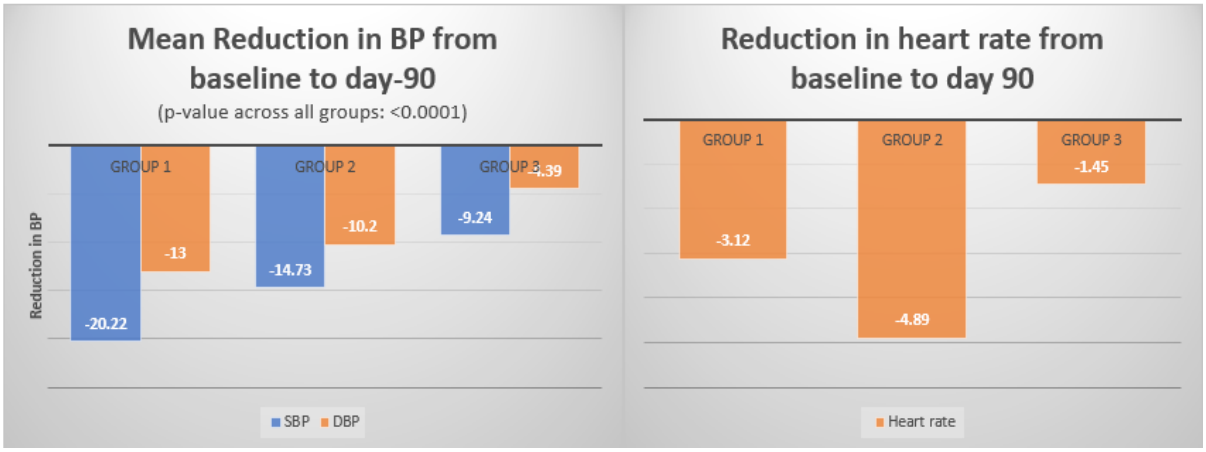


Figure 3: Summary of reduction in average SBP/DBP and heart rate from baseline to final visit (day-90)

		Count (N=133)			**Inter Group p-Value**		
Change in SBP/ DBP from baseline at	**Standing**	**Group 1 (N=50)**	**Group 2 (N=45)**	**Group 3 (N=38)**	**Group 1 vs 2**	**Group 1 vs 2**	**Group 1 vs 2**
Baseline visit 1	SBP	156.06 ± 20.19	147.13 ± 19.42	144.55 ± 14.19	0.0309	0.0037	0.5004
Day-90	SBP	132.58 ± 9.11	132.33 ± 10.62	137.89 ± 12.48	0.9020	0.2534	0.2568
Reduction in SBP from baseline	SBP	-23.4 ± 20.32	-14.8 ± 20.63	-6.66 ± 13.21	0.0309	<0.0001	0.0393

Intragroup P-value	SBP	<0.0001	<0.001	0.0041			
Baseline visit 1	DBP	92.18 ± 11.00	87.83 ± 12.36	86.63 ± 8.31	0.0727	0.0114	0.6135
Day-90	DBP	81.56 ± 5.28	80.20 ± 6.91	84.24 ± 8.8	0.7748	0.1121	0.1105
Reduction in DBP from baseline	DBP	-10.68 ± 10.8	-7.53 ± 13.58	-2.39 ± 8.24	0.2119	<0.001	0.0449
Intragroup P-value	DBP	<0.0001	0.0006	0.0854			

Table 1: Summary of the difference in the mean BP (SBP/DBP) from baseline to Day-90 (Final visit) in standing position.

Mean reduction in SBP/DBP for visit-2,4 and 6 in sitting and standing positions for each group is provided in (Table 2).

		Count (N=133) **Mean difference in the Sitting BP (SBP/DBP) mmHg**			**Count (N=133)** **Mean difference Standing BP (SBP/DBP)mmHg**		
Visit Day		**Group 1 (N=50)**	**Group 2 (N=45)**	**Group 3 (N=38)**	**Group 1 (N=50)**	**Group 2 (N=45)**	**Group 3 (N=38)**
Day-30(visit 2)	SBP	-18.06	-11.13	-6.08	-18.08	-11.76	-7.00
	DBP	-10.06	-8.71	-4.68	-7.94	-4.71	-4.34
Day-60(visit 4)	SBP	-19.90	-13.36	-8.05	-24.30	-13.51	-5.66
	DBP	-12.08	-8.96	-5.29	-11.10	-6.49	-3.00
Day-90(visit 6)	SBP	-22.22	-14.73	-11.39	-23.40	-14.80	-9.55
	DBP	-13.00	-10.20	-5.79	-10.68	-7.53	-3.63

Table 2: Summary of the difference in the mean Sitting and Standing BP (SBP/DBP) from baseline at Day- 30, 60, and 90.

Figure 4 and 5 show trends of systolic and diastolic BP (sitting and standing) along with delta change across the visits.

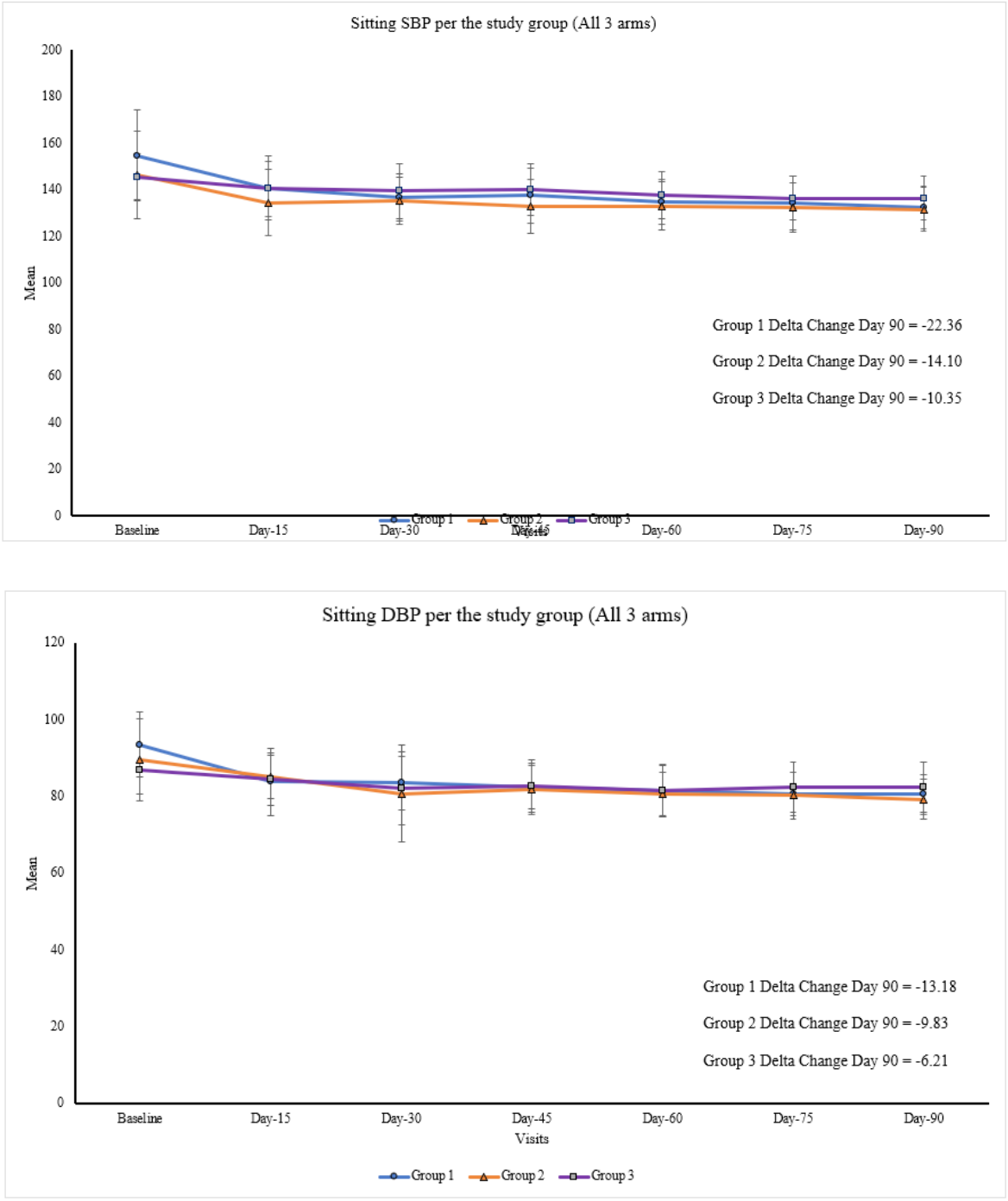


Figure 4: Comparison of Mean of Sitting SBP and DBP per the study group (All 3 arms)

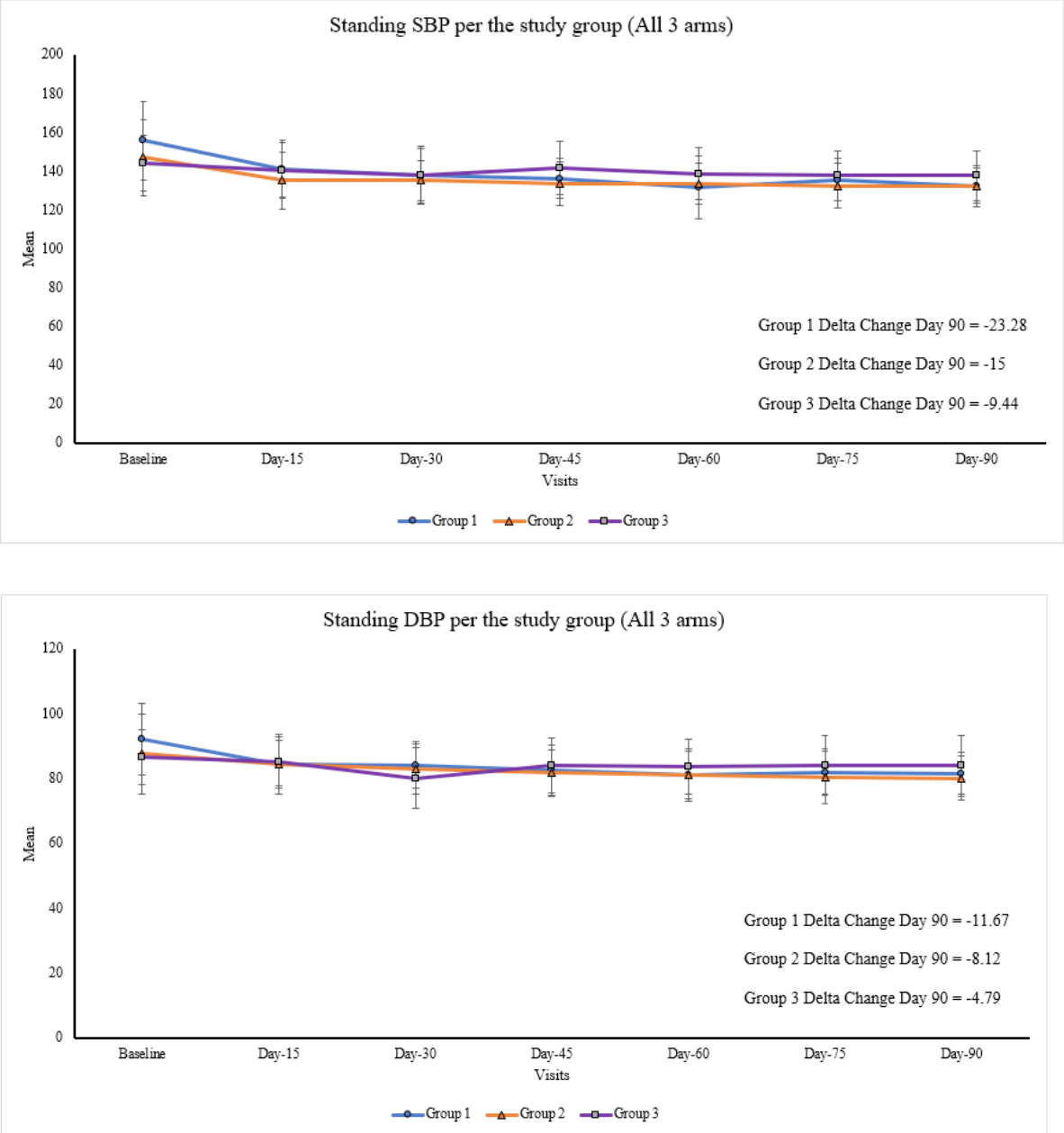


Figure 5: Comparison of Mean of Standing SBP and DBP per the study group (All 3 arms)

There was no statistically significant difference in sitting and standing SBP/DBP across all the visits for the three study groups.

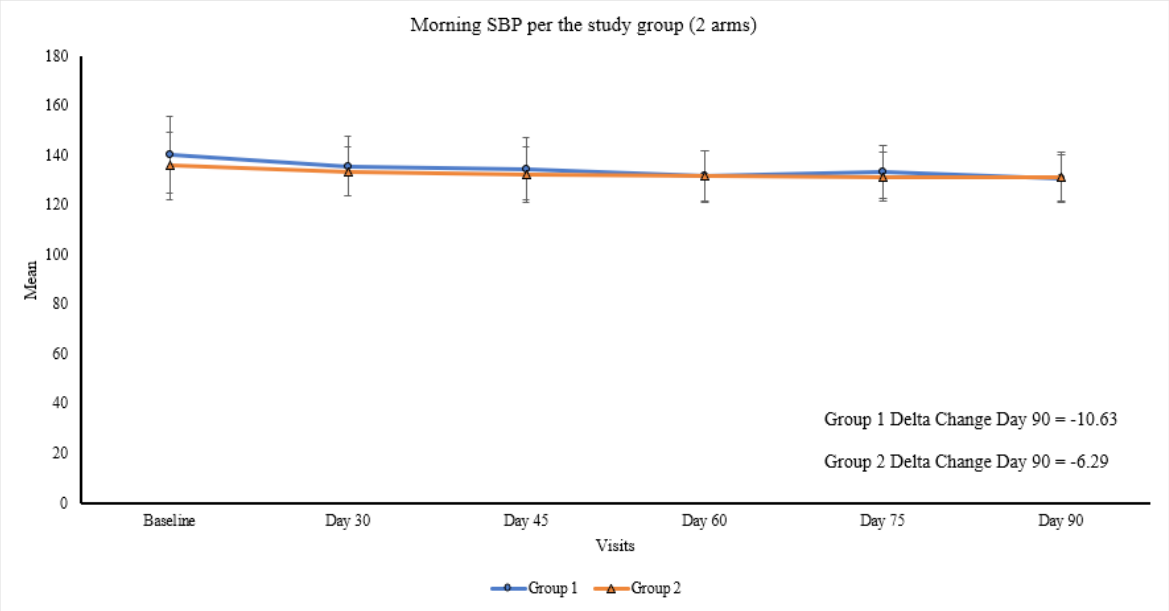
Repeated analysis of variance (ANOVA measure) and Dunnett's multiple comparison test for group1-3

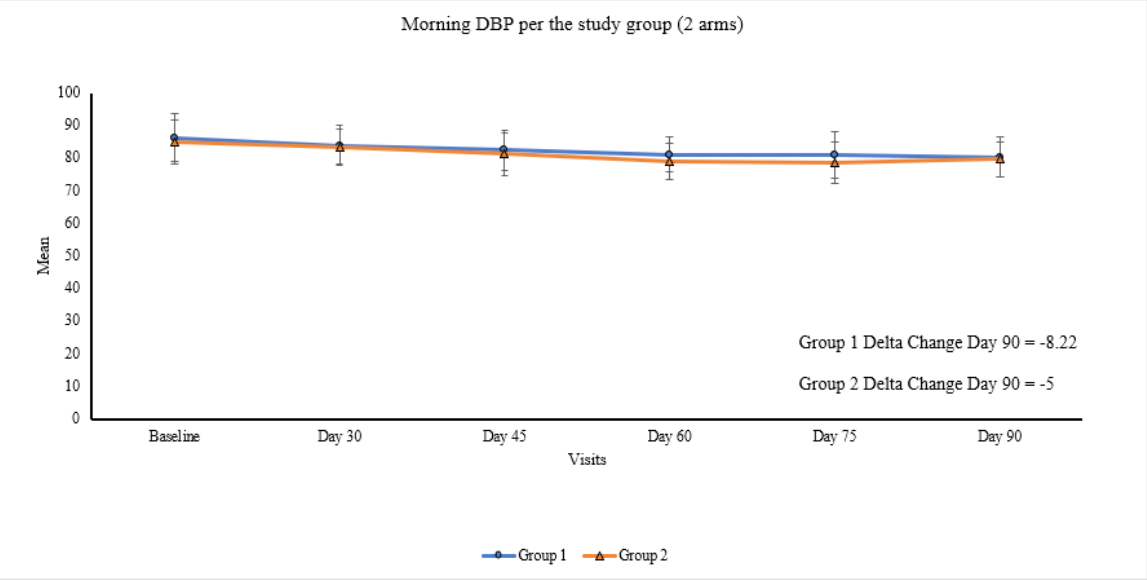
ANOVA measure for sitting and standing SBP/DBP for groups 1 and 2, and SBP of group 3 showed $p < 0.05$. For group 3 DBP sitting had ($p = 0.019$) and standing ($p = 0.270$).

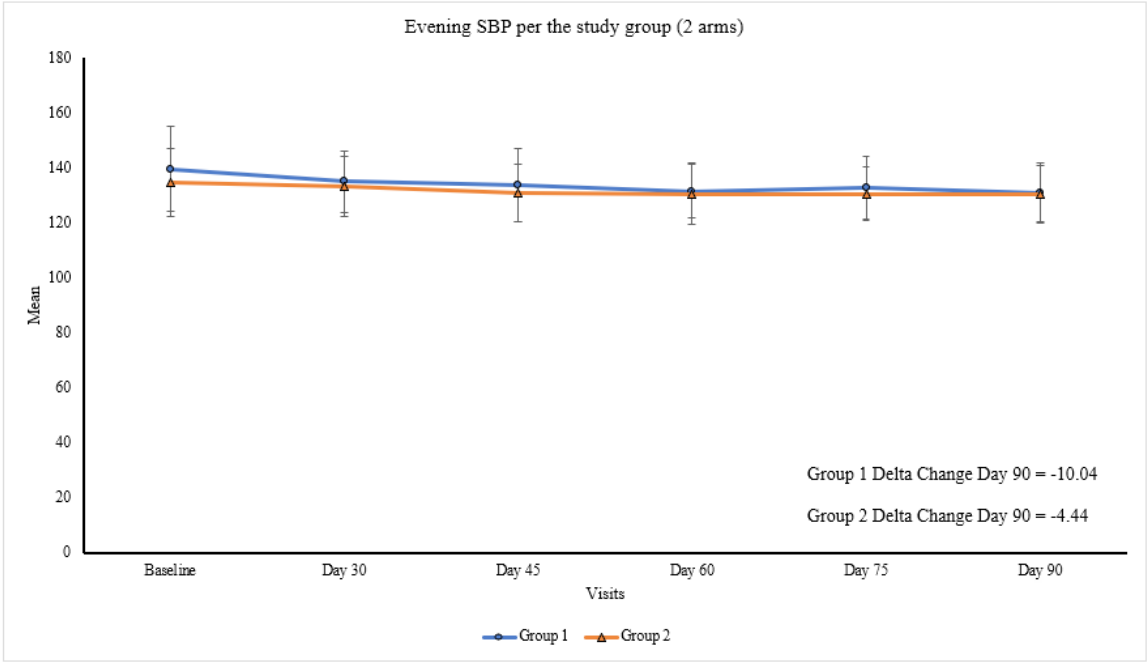
Dunnett's multiple comparison tests for sitting and standing SBP/DBP at each FUP (1- 6) for groups 1 and 2 showed $p < 0.05$. For group 2 FUP-1 of standing DBP, it showed $p > 0.05$. Dunnett's multiple comparison tests showed variation in P value across the FUP visits in sitting and standing SBP/DBP for group 3.

Comparison in clinic BP and BP through HBPM

The HBPM data of day-2 is presented in (Figure 6) (HBPM data for day 3 and 4 are presented in (supplement Table 2). A significant reduction in both SBP and DBP was noted in group 1 and 2. Also, a comparison between morning and evening BP showed a statistically significant reduction.







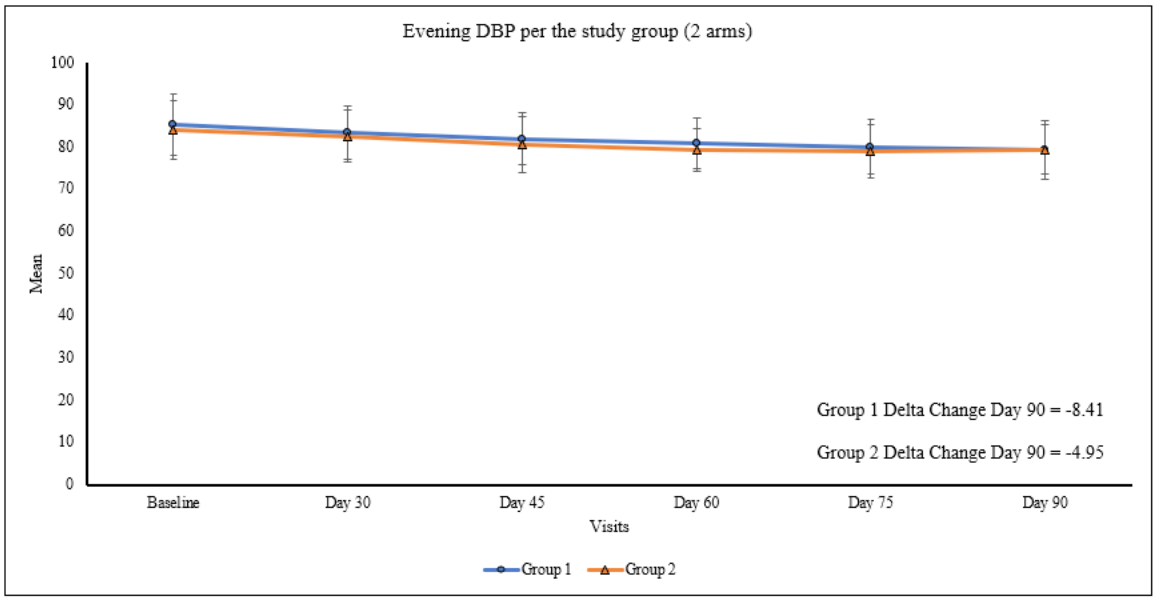


Figure 6: Comparison of Mean of Morning and Evening SBP/DBP through HBPM (day 2) per the study group (2 arms)

PARAMETER	Count (N=95)		
	Group 1 (N=50)	Group 2 (N=45)	Inter Group p-Value
			Group 1 VS 2
Day -3 [Morning SBP mean]			
FU visit 1	140.69 ± 16.08	136.10 ± 13.36	0.1360
FU visit 6	131.62 ± 9.96	131.11 ± 10.62	0.8097
Change from Visit 1	-9.07	-4.99	0.0545
p-value	<0.0001	0.0006	
Day -3 [Morning DBP mean]			
FU visit 1	86.56 ± 8.00	85.37 ± 8.47	0.4832
FU visit 6	80.62 ± 7.08	80.16 ± 6.00	0.7349
Change from Visit 1	-5.94	-5.21	0.1632
p-value	<0.0001	0.0018	NA
Day -3 [Evening SBP mean]			
FU visit 1	140.29 ± 17.45	134.89 ± 13.70	0.0994
FU visit 6	131.05 ± 10.35	130.21 ± 10.78	0.6994
Change from visit 1	-9.24	-4.68	0.1762
p-value	<0.0001	0.0005	NA
Day -3 [Evening DBP mean]			
FU visit 1	85.83 ± 8.64	83.20 ± 11.13	0.1991
FU visit 6	79.38 ± 8.26	78.87 ± 6.42	0.7396
Change from visit 1	-6.45	-4.33	0.0531
p-value	<0.0001	0.0006	NA
Day -4 [Morning SBP mean]			
FU visit 1	138.41 ± 14.94	135.24 ± 13.76	0.2866
FU visit 6	130.72 ± 10.92	130.94 ± 10.30	0.9200
Change from Visit 1	-7.69	-4.3	0.1934
p-value	<0.0001	0.0052	NA
Day -4 [Morning DBP mean]			
FU visit 1	84.94 ± 8.05	84.47 ± 6.33	0.7543
FU visit 6	80.56 ± 6.76	79.86 ± 5.64	0.5873
Change from Visit 1	-4.38	-4.61	0.5676
p-value	<0.0001	0.0011	NA
Day -4 [Evening SBP mean]			
FU visit 1	137.48 ± 16.50	134.24 ± 12.67	0.2898
FU visit 6	131.46 ± 12.48	130.83 ± 10.95	0.7952
Change from Visit 1	-6.02	-3.41	0.3254
p-value	<0.0001	0.0007	NA
Day -4 [Evening DBP mean]			
FU visit 1	83.76 ± 8.11	83.93 ± 5.94	0.9622

PARAMETER	Count (N=95)		
FU visit 6	79.34 ± 7.91	80.21 ± 6.38	0.5594
Change from Visit 1	-4.42	-3.72	0.4435
p-value	<0.0001	0.0019	NA

Table 2: Summary of changes in BP through HBPM (Day 3 and 4, morning and evening BP)

Group 1: (N=50)

At the baseline, the mean SBP/DBP at the clinic was 158.60 (± 18.96)/ 97.06 (± 6.22), and through HBPM was 140.04 (± 15.18)/ 85.86 (± 7.17) with p-value <0.0001. On day 90, the mean SBP/DBP at the clinic was 132.58 (± 9.11)/ 80.56 (± 5.28) and through HBPM was 131.10 (± 10.05)/ 79.92 (± 6.34) with p-value of (SBP/DBP) 0.4423/0.5846. The reduction was statistically significant from baseline to day 90 in the mean SBP/DBP at the clinic and through HBPM and it was 26.02 ($p < 0.0001$)/ 16.5 ($p < 0.0001$) and 8.94 ($p < 0.0001$)/ 5.64 (p - 0.0020), respectively.

Group 2: (N=45)

At the baseline, the mean SBP/DBP at the clinic was 155.18 (±17.57) / 96.44 (±7.30) and through HBPM was 135.31 (±12.72) / 84.56 (±6.52) with intergroup p-value (SBP/DBP) of < 0.0001. On day 90, the mean SBP/DBP at the clinic was 131.67 (±9.57) / 79.29 (±5.30) and through HBPM was 128.01(±22.01) / 86.24 (±5.93) with an intergroup p-value of SBP/DBP (0.3091 / <0.0001). A statistically significant reduction was seen from baseline to day 90 in the mean SBP/DBP at the clinic and through HBPM, it was 23.51 ($p < 0.0001$)/ 17.15 ($p <0.0001$) and 7.3 ($p < 0.05$)/ 1.68 (p-value < 0.05), respectively.

A comparison between the number of subjects achieving target BP through Clinic BP and HBPM is presented in (Table 3).

	Clinic BP	HBPM	Intergroup p-value
Group 1 (N=45)			
Day 15	10(20.00 %)	13(26.00 %)	0.4759
Day 30	12(24.00 %)	19(38.00 %)	0.1301
Day 45	13(26.00 %)	19(38.00 %)	0.1984
Day 60	13(26.00 %)	18(36.00 %)	0.2797
Day 75	13(26.00 %)	22(44.00 %)	0.0592
Group 2 (N=38)			
Day 15	16(35.56 %)	5(11.11 %)	0.0061
Day 30	14(31.11 %)	17(37.78 %)	0.5057
Day 45	19(42.22 %)	20(44.44 %)	0.8315
Day 60	17(37.78 %)	20(44.44 %)	0.5204
Day 75	18(40.00 %)	21(46.67 %)	0.5234

Table 3: Summary of Patients Achieving Target Blood Pressure Clinic BP and Average HBPM in 'Group 1' and 'Group 2'

Visit	No. of subjects achieving (%) BP per the study group (standing position)					
	Group 1 N=50		Group 2 N=45		Group 3 N=38	
Standing	**140/90 mmHg**	**130/80 mmHg**	**140/90 mmHg**	**130/80 mmHg**	**140/90 mmHg**	**130/80 mmHg**
Day-15	21 (42 %)	5 (10 %)	23 (51.11 %)	6 (13.33 %)	17 (44.74 %)	4 (10.53 %)
Day-30	25 (50 %)	4 (8 %)	23 (51.11 %)	6 (13.33 %)	19 (50 %)	5 (13.16 %)
Day-45	24 (48 %)	8 (16 %)	28 (62.22 %)	9 (20 %)	14 (36.84 %)	6 (15.79 %)
Day-60	32 (64 %)	11 (22 %)	30 (66.67 %)	10 (22.22 %)	19 (50 %)	8 (21.05 %)
Day-75	31 (62 %)	6 (12 %)	31 (68.89 %)	13 (28.89 %)	20 (52.63 %)	7 (18.42 %)
Day-90	32 (64 %)	9 (18 %)	33 (73.33 %)	13 (28.89 %)	20 (52.63 %)	7 (18.42 %)

Supplement Table 3: Summary of Patient % achieving target BP of 130/80 and 140/90 mmHg per visit (standing position)

No changes in the subject prescriptions were observed in the study across all three arms.The QoL assessment did not report any difference in the groups, and subjects with HBPM were satisfied.

The laboratory parameters data were not available for all subjects. The available data did not indicate any statistically or clinically significant changes in the mean value from the baseline to the final visit. Data for laboratory parameters are presented in (Table 4).

Parameters	Group 1	Group 2	Group 3
Serum Creatinine (mg/dL)	-0.02 (n=31)	+0.23 (n=29)	-0.07 (n=29)
Serum Sodium (mEq/L)	+1.32 (n=31)	+ 0.21 (n=29)	+0.48 (n=29)
Serum Potassium (mEq/L)	+0.02 (n=30)	+0.13 (n=29)	+0.03 (n=29)
HbA1c (%)	-0.32 (n=29)	- 0.13 (n=28)	- 0.12 (n=27)
FPG (mg/dL)	-7.21 (n=25)	-2.99 (n=23)	+13.13 (n=26)
Total Cholesterol (mg/dL)	-8.32 (n=31)	-18.69 (n=29)	-9.69 (n=29)
HDL Cholesterol (mg/dL)	+17.65(n=31)	-17.91 (n=29)	+6.76 (n=29)
LDL Cholesterol (mg/dL)	-2.51 (n=31)	-15.5 (n=29)	-5.81 (n=29)
VLDL Cholesterol (mg/dL)	+0.01 (n=31)	-32.21 (n=29)	-2.72 (n=29)
Triglycerides (mg/dL)	+2.48 (n=31)	-5.45 (n=29)	-7.95 (n=29)

Table 4: Summary of change in the laboratory parameters (mean) from baseline to final visit.

Adverse events

No adverse events were reported in this study requiring discontinuation. One subject in each group 1 and 2 reported limb numbness and one from group 3 reported mild pedal edema.

Details of the standard of care received

Details of the standard of care received for HTN management were available for 36 subjects. Of these, 3 (8.33%) received ARBs; CCBs were given to 2 (5.55 %); 8 (22.2%) received CCB + β-Blocker; CCB + ARB's, and CCB + Diuretic were received by 6 (16.66%), each; 5 (13.88%) subjects received β-Blockers; 3 (8.33%) were treated with CCB + Diuretic; 2 (5.56 %) were treated with ARB + diuretic, and one subject (2.77 %) was treated with ARB + CCB + diuretic.

Discussion

The principal findings of our study are a clinically and statistically significant reduction in the SBP and DBP in the patients receiving dual combination therapy in a single pill, with no reported cases of hypotension or orthostatic hypotension after treatment initiation, and patients' acceptance of monitoring of home BP.

Studies have observed that the SBP/DBP through HBPM were more reliable as compared to office and clinic BP [7], with no significant difference from ABPM [8], more strongly associated with left ventricular mass index [7], and most accepted by patients [9], supporting its utility in primary care practice. These findings concur with our study observations where subjects were satisfied and showed acceptability to HBPM.

The use of self-measured BP monitoring is associated with better BP control, and the benefits of BP lowering with self-measured BP monitoring are greatest when it is conducted with co-interventions [5]. Our study observed more subjects achieved target BP recordings through HBPM as compared to clinic BP.

Volpe M et al reported that the combination of olmesartan medoxomil (10-40mg) with amlodipine 5mg for 8 weeks (double-blind) reduced mean SBP/DBP by up to 16.8 mmHg and 9.6 mmHg, respectively, and the combination is effective and well tolerated in reducing BP in patients with moderate to severe hypertension [10].Our study findings corresponds with the above observations, our study demonstrated a statistically significant reduction in SBP/DBP in sitting and standing positions by 26.02/16.5 and 26.52/14.9, respectively, in the patients receiving olmesartan/amlodipine (20/5mg).

An analysis by Bilo G et al reported that the combination of amlodipine with the ARB olmesartan decreased not only 24-h BP levels but also early morning and morning BP levels, which are important to prevent early morning cardiovascular events associated with morning surge in BP [11].The analysis reported the early morning reduction in BP with olmesartan/amlodipine (20mg/5mg) combination over 8 weeks was (SBP/DBP) 12.24/9.22 [17]. Our study reported the reduction in morning BP captured through HBPM at day 2, 3, 4 for Olmesartan/Amlodipine (20/5mg) treatment arm as [SBP/DBP: 11.14/7.38, 9.07/5.94, and 7.69/4.38], respectively. For the same time points morning reduction observed through HBPM in the patients on treatment arm Olmesartan/CTLD were 5.3/5.95, 4.99/5.21, and 4.3/4.61,

respectively, which was comparatively lower.

OLAS study evaluated the effects of treatment with Olmesartan/amlodipine and Olmesartan /hydrochlorothiazide and reported that BP decreased significantly in each group vs baseline (P<0.001) but there were no significant differences in BP control between the groups (analysis of variance, P=0.39) [12].These findings are similar to our study findings which demonstrated a statistically significant reduction in BP through HBPM as well as clinic BP with Olmesartan/Amlodipine(20/5mg), and Olmesartan/CTLD(20/6.25mg) treatment group. However, the OLAS study did not include patients with DM, whereas 42.10% of patients from our study had DM.

Filipova E et al conducted a meta-analysis to compare the efficacy of the combination of ARB and CTLD to the combination of ARB and hydrochlorothiazide in patients with hypertension and suggested a small but significant favor for CTLD in BP control when compared to hydrochlorothiazide [13].

Guidelines by AAFP observed that BP targets of 140 mmHg systolic and 90 mmHg diastolic offer similar reduction in cardiovascular and all-cause mortality as lower targets and have fewer adverse effects [14]. Park S suggested that the first target of anti-hypertensive treatment should be to achieve BP lowering below 140/90 mmHg. Once that target is achieved, one could target BP below 130/80 mmHg keeping in mind to avoid signs of organ hypoperfusion [15]. In the present study 80%, and 77.78% of the patients from group 1, and 2 achieved 140/90mmHg of BP at the final visit.

At ages 40–69 years, each difference of 20 mm Hg usual SBP (or, approximately equivalently, 10 mm Hg usual DBP) is associated with more than a twofold difference in the stroke death rate, and in the death rates from IHD and from other vascular causes [16]. In our TIME-AIM study, at 90-days subjects across all three study arms showed a statistically significant reduction in mean SBP/DBP from the baseline. However, subjects receiving combination therapy of 'Olmesartan/Amlodipine(20/5mg)' and 'Olmesartan/CTLD (20/6.25mg)', demonstrated a better reduction in SBP/DBP by 26.02/16.5, 26, and 23.51/17.15, respectively. Whereas standard-of-care treatment reported a mean reduction of 14.53/13.06.

It was noted that fewer patients reached target BP when the target was low (130/80mmHg) as compared to a target of 140/90mmHg. There could be several reasons for this. One important reason could be clinical inertia – "sticking to the principle of being careful"; which may be addressed by a continued appreciation of safety of lower BP target in several groups of patients.

Diuretics are considered to be one of the main determinants of drug-related orthostatic hypotension, particularly in older adults [17]. However, our study did not observe any events of orthostatic hypotension in the patients receiving the combination of 'Olmesartan/CTLD(20/6.25mg)'

Our study findings observed that the reduction in SBP/DBP in patients on combination therapy was better than in the subjects receiving standard of care. Clinicians participating in the study reported good acceptance to combination therapy and noted that the subjects were comfortable using HBPM.

In our study there was a statistically significant difference in the mean baseline BP obtained through HBPM and clinic BP. However, after treatment initiation over the period 90 days, BP reported through HBPM, and clinic BP did not show any significant difference and the results were comparable.

Study limitations

A small sample size, short study duration, and susceptibility to bias because of the real-world study design were few of the study limitations. Although we aimed for an equal number of patients in each study group, at the final analysis group-3 had fewer patients (N=38). However, the effectiveness of the combination therapy was tested against the baseline BP.

Conclusion

Our study demonstrated that combination therapy with Olmesartan/Amlodipine(20/5mg)' and 'Olmesartan/CTLD(20/6.25mg)' is effective and safe in significantly reducing BP in Indian patients with uncontrolled BP and treatment naïve patients diagnosed with stage 2 de novo hypertension in real-world set up with good acceptability of HBPM.

Funding: None

Conflict of Interest: None

Ethics Approval: The study was approved by the independent ethics committee of Gurushree High Tech multi-specialty hospital, Bengaluru on 15 June 2022.

Patient Consent: The patient was shared with IDC and the same was signed by them or by their legal guardian.

Clinical Trail Registration No: CTRI/2022/08/045116

Data Availability Statement: The data that support the findings of this study are available on request from the author, ND. The data are not publicly available due to [restrictions e.g. their containing information that could compromise the privacy of research participants].

References

1. Shah SN, Munjal YP, Kamath SA, Wander GS, Mehta N, et al. (2020) Indian guidelines on hypertension-IV (2019). J Hum Hypertens. 34:745–758.

2. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, et al. (2023) 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 41:1874-2071.

3. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, et al. (2020) 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 75:1334-1357.

4. Guideline for the pharmacological treatment of hypertension in adults. (2021) World Health Organization.

5. Shimbo D, Artinian NT, Basile JN, Krakoff LR, Margolis KL, et al. (2020) Self-Measured Blood Pressure Monitoring at Home: A Joint Policy Statement From the American Heart Association and American Medical Association. Circulation. 142: e42–63.

6. An J, Derington CG, Luong T, Olson KL, King JB, et al. (2020) Fixed-Dose Combination Medications for Treating Hypertension: A Review of Effectiveness, Safety, and Challenges. Curr Hypertens Rep. 22: 95.

7. Schwartz JE, Muntner P, Kronish IM, Burg MM, Pickering TG, et al. (2020) Reliability of Office, Home, and Ambulatory Blood Pressure Measurements and Correlation with Left Ventricular Mass. J Am Coll Cardiol. 76: 2911–2922.

8. Green BB, Anderson ML, Cook AJ, Ehrlich K, Hall YN, et al. (2022) Clinic, Home, and Kiosk Blood Pressure Measurements for Diagnosing Hypertension: A Randomized Diagnostic Study. J Gen Intern Med. 37:2948–56.

9. Thompson MJ, Anderson ML, Cook AJ, Ehrlich K, Hall YN, et al. (2023) Acceptability and Adherence to Home, Kiosk, and Clinic Blood Pressure Measurement Compared to 24-H Ambulatory Monitoring. J Gen Intern Med. 38:1854–61.

10. Volpe M, Brommer P, Haag U, Miele C (2009) Efficacy and tolerability of olmesartan medoxomil combined with amlodipine in patients with moderate to severe hypertension after amlodipine monotherapy: a randomized, double-blind, parallel-group, multicentre study. Clin Drug Investig. 29(1):11–25.

11. Bilo G, Koch W, Hoshide S, Parati G (2014) Efficacy of olmesartan/amlodipine combination therapy in reducing ambulatory blood pressure in moderate-to-severe hypertensive patients not controlled by amlodipine alone. Hypertens Res. 37:836–844.

12. Martinez-Martin FJ, Rodriguez-Rosas H, Peiro-Martinez I, Soriano-Perera P, Pedrianes-Martin P, et al. (2011) Olmesartan/amlodipine vs olmesartan/hydrochlorothiazide in hypertensive patients with metabolic syndrome: the OLAS study. J Hum Hypertens. 25:346–353.

13. Filipova E, Dineva S, Uzunova K, Pavlova V, Kalinov K, Vekov T (2020) Combining angiotensin receptor blockers with chlorthalidone or hydrochlorothiazide - which is the better alternative? A meta-analysis. Syst Rev. 9:195.

14. Arnold MJ (2022) Blood Pressure Targets in Adults with Hypertension: Guidelines From the AAFP. Am a Fam Physician. 106:721–722.

15. Park S (2019) Ideal Target Blood Pressure in Hypertension. Korean Circ J. 49:1002–1009.

16. Lewington S, Clarke R, Qizilbash N, Peto R, et al. (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 360:1903–1913.

17. Rivasi G, Rafanelli M, Mossello E, Brignole M, Ungar A (2020) Drug-Related Orthostatic Hypotension: Beyond Anti-Hypertensive Medications. Drugs Aging. 37: 725–738.