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Comparative Evaluation of Lercanidipine and Amlodipine in Hypertensive Patients: Efficacy, Tolerability, and the Role of Gut Microbiota Modulation

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ABSTRACT

Background: Hypertension affects over 1.28 billion adults globally and is a major contributor to cardiovascular morbidity and mortality. Calcium channel blockers, such as lercanidipine and amlodipine, are widely prescribed for hypertension management, yet their differential impact on gut microbiota remains underexplored.

Objective: This study aimed to compare the efficacy, tolerability, and microbiota-modulating effects of lercanidipine versus amlodipine in hypertensive patients over a 12-month period.

Methods: A randomized, open-label clinical trial was conducted at three tertiary care hospitals in Peshawar, Pakistan, involving 320 adults with essential hypertension. Participants were randomly assigned to receive either lercanidipine 10 mg or amlodipine 5 mg once daily. Blood pressure was monitored monthly, and treatment adherence, adverse effects, and gut microbiota changes were assessed. Stool samples were collected at baseline and after 12 months for 16S rRNA sequencing. Statistical comparisons were made using t-tests, ANOVA, and Kaplan–Meier survival analysis.

Results: Both groups exhibited significant reductions in systolic and diastolic blood pressure, with lercanidipine achieving target levels faster (4.2 vs. 5.6 weeks). Lercanidipine was associated with higher adherence (92% vs. 85%) and fewer cases of peripheral edema (5% vs. 12%). Gut microbiota analysis revealed that lercanidipine preserved alpha diversity and enriched beneficial genera such as *Faecalibacterium* and *Lactobacillus*, whereas amlodipine led to decreased diversity and an increase in *Escherichia/Shigella* abundance.

Conclusion: Both drugs work well to lower blood pressure, yet lercanidipine has a better chance of tolerance, quicker action on blood pressure and helps improve gut bacteria. These findings suggest its potential as a preferable choice in personalized hypertension management, participating microbial health consideration.

Keywords: *Hypertension, Lercanidipine, Amlodipine, Blood Pressure, Tolerability, Gut Microbiota, Calcium Channel Blockers*

1. INTRODUCTION

Hypertension is a big health problem across the globe, impacting almost 1.28 billion adults aged 30–79 years and the majority of these cases occur in low- and middle-income countries [1]. While it's possible to manage hypertension with available treatments, fewer than half of those with hypertension receive a diagnosis, less than 4 in 10 get treatment and only one in five achieve the needed blood pressure level [2].

More people now have hypertension because there are aging populations, live in cities, use junk food, live less active lives,

sedentary lifestyle and/or experience higher levels of stress [5]. In Pakistan, experts predict that the number of people with hypertension could rise from 30.5% in 2015 to 32.9% by 2040, requiring attention to control measures [4].

Calcium channel blockers (CCBs) are a major treatment for high blood pressure. They achieve this effect by decreasing calcium that enters vascular smooth muscle, leading to increased blood flow and lowered blood pressure [5]. Many physicians often prescribe amlodipine and lercanidipine from the dihydropyridine group because they are both effective and can be taken only once each day [6].

Due to its slow action and being present in the system for a long period, amlodipine is prescribed only once each day [7]. It is proven to drop blood pressure and tends to have a good track record of safety. Even so, some of the usual side effects are peripheral edema, dizziness and palpitations [8,9].

Because lercanidipine is highly lipophilic and acts mainly on blood vessels, it has a slow start and a long effect on the body [10]. Because of its pharmacokinetics, it shows more effectiveness for lowering blood pressure and reducing swelling in the limbs than other CCBs [11,12].

Scientific studies now highlight that the health of our gut microbiota is connected to our blood pressure as well as other aspects of heart health [13]. Studies show that changes in the gut's microbial community may be related to high blood pressure, possibly through how the immune system works, metabolism and production of crucial substances [14,15]. There is evidence that some medicines for high blood pressure may have an impact on the bacteria in the gut, possibly changing how treatment works [16,17].

Although many patients take amlodipine or lercanidipine, few studies compare how they affect the gut microbiome. Getting to know these types of interactions matters because they can alter how effective or well-tolerated a drug is and they may also have a role in patient's overall cardiac health [18,19].

This study is designed to compared lercanidipine and amlodipine for effectiveness, tolerability and the role of gut microbiota in hypertensive patients. The aim is to combine clinical results with microbiota research to offer new hypertension management approaches for different individuals.

2. METHODOLOGY

This study was organized as a 12-month, randomized, open-label, parallel-group clinical trial at three tertiary care centers in Peshawar, Pakistan: Khyber Teaching Hospital Peshawar, Lady Reading Hospital Peshawar and Hayatabad Medical Complex Peshawar, from January 2023 to June 2024. There were 320 adult patients ages 30 to 65 diagnosed with essential hypertension who took part after providing an informed consent. Hypertension was defined as a systolic blood pressure (SBP) of ≥140 mmHg and/or a diastolic blood pressure (DBP) of ≥90 mmHg measured on two separate occasions according to current international guidelines. Eligible patients had not received antihypertensive treatment in the previous month and had a body mass index (BMI) ranging from 18.5 to 35 kg/m². Patients were excluded if they had secondary hypertension, stage 3 or higher chronic kidney disease, significant hepatic dysfunction, a history of major cardiovascular events in the past six months, gastrointestinal conditions known to affect the gut microbiota such as inflammatory bowel disease, recent (within three months) use of antibiotics or probiotics, or if they were pregnant or lactating.

Participants were randomized using a computer-generated sequence into two equal groups of 160 patients each. One group received lercanidipine 10 mg once daily, while the other group received amlodipine 5 mg once daily. Patients attended monthly follow-up visits for monitoring of blood pressure, medication adherence (assessed through pill counts and patient diaries), and adverse events, including common side effects such as peripheral edema, dizziness, or headache. Blood pressure was measured using an automated sphygmomanometer after a 10-minute rest in a seated position, and three readings were averaged for analysis. The primary efficacy endpoint was the change in SBP and DBP from baseline to 12 months. Other primary outcomes included the time required to achieve target BP (<140/90 mmHg), adherence rate, tolerability profile, and incidence of adverse effects.

To assess the impact of treatment on gut microbiota, stool samples were collected at baseline and after 12 months of treatment. Samples were immediately preserved in nucleic acid stabilizing buffer and stored at −80°C until analysis. DNA was extracted using standardized kits, and the V3–V4 regions of the 16S rRNA gene were amplified and sequenced on an Illumina MiSeq platform. Bioinformatic analysis was conducted using QIIME2, with alpha diversity assessed through Shannon and Simpson indices, and beta diversity analyzed via Bray–Curtis dissimilarity. LEfSe (Linear Discriminant Analysis Effect Size) was employed to identify taxa that significantly differed between treatment groups.

Statistical analyses were performed using SPSS version 26.0. Continuous variables were presented as mean ± standard deviation and compared using independent sample t-tests or analysis of variance (ANOVA), while categorical variables were analyzed with chi-square or Fisher's exact test. Kaplan–Meier survival curves were plotted to assess the time to achieve target blood pressure, and microbiota compositional differences were evaluated using PERMANOVA. A two-tailed p-value of <0.05 was considered statistically significant. The study was approved by the Institutional Review Boards of all participating centers and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP)

guidelines.

3. RESULTS

A total of 320 hypertensive patients were randomized into two equal groups receiving either lercanidipine or amlodipine. The baseline characteristics of both groups were comparable with no statistically significant differences in age, gender distribution, BMI, or baseline systolic and diastolic blood pressure (Table 1).

Over the 12-month follow-up, both groups demonstrated significant reductions in systolic and diastolic blood pressures. However, the lercanidipine group achieved target BP more rapidly, with a mean time of 4.2 weeks compared to 5.6 weeks in the amlodipine group (Figure 1). BP reductions were sustained across both groups, but the lercanidipine group consistently showed slightly lower final values (Table 2).

Adherence to medication was notably higher in the lercanidipine group (92%) compared to the amlodipine group (85%), as illustrated in Figure 2. This corresponded with a lower incidence of adverse effects, particularly peripheral edema, which was significantly more common in the amlodipine group (Figure 3; Table 3).

Gut microbiota analysis revealed marked differences between the two treatment arms. At 12 months, patients receiving lercanidipine maintained higher alpha diversity scores, indicating a healthier and more resilient gut microbiome (Figure 4). In contrast, the amlodipine group showed a decline in microbial diversity from baseline, with a shift toward pro-inflammatory bacterial profiles.

Additional microbiota-related figures (Figures 5 to 8), including beta diversity plots, phylum-level abundance, heatmaps, and taxa correlations with blood pressure reduction, further supported these trends. Figure 5 illustrates the beta diversity analysis of gut microbiota using a Principal Coordinates Analysis (PCoA) plot based on Bray-Curtis dissimilarity at 12 months. Each point represents the microbial profile of an individual participant, with blue dots and orange dots. This visual distinction supports the hypothesis that the choice of antihypertensive agent influences microbial community structure. Figure 6 shows the relative abundance of major gut bacterial phyla at 12 months, comparing the lercanidipine and amlodipine groups. Lercanidipine preserved a more balanced Firmicutes/Bacteroidetes ratio and limited Proteobacteria expansion, suggesting a healthier microbial profile. The heatmap in Figure 7 illustrates higher levels of *Lactobacillus* and *Faecalibacterium* in the lercanidipine group, and a pronounced abundance of *Escherichia/Shigella* in the amlodipine group, suggesting differential impacts on gut microbial profiles. Figure 8 illustrates the correlation between changes in key gut microbial taxa and reductions in systolic blood pressure. Positive correlations were observed for *Faecalibacterium* and *Lactobacillus*, suggesting their potential role in blood pressure modulation.

Overall, the data indicate that while both drugs are effective in lowering blood pressure, lercanidipine provides advantages in terms of tolerability, adherence, and gut microbiota preservation.

Table 1: Baseline Characteristics of Participants

Variable	Lercanidipine Group (n=160)	Amlodipine Group (n=160)	p-value
Age (years)	54.2	53.8	0.57
Male (%)	55	53	0.68
BMI (kg/m²)	26.4	26.1	0.39
SBP (mmHg)	152.3	153.1	0.44
DBP (mmHg)	95.2	95.6	0.61

Table 2: Changes in Blood Pressure Over 12 Months

Timepoint	Lercanidipine SBP (mmHg)	Lercanidipine DBP (mmHg)	Amlodipine SBP (mmHg)	Amlodipine DBP (mmHg)

Baseline	152.3	95.2	153.1	95.6
6 Months	138.2	87.3	139.4	88.7
12 Months	132.1	82.5	133.5	84.2

Table 3: Incidence of Adverse Effects

Adverse Effect	Lercanidipine (n=160)	Amlodipine (n=160)	p-value
Peripheral Edema	8	20	0.004
Headache	10	15	0.22
Dizziness	7	10	0.34

Figure 1: Time to Achieve Target Blood Pressure

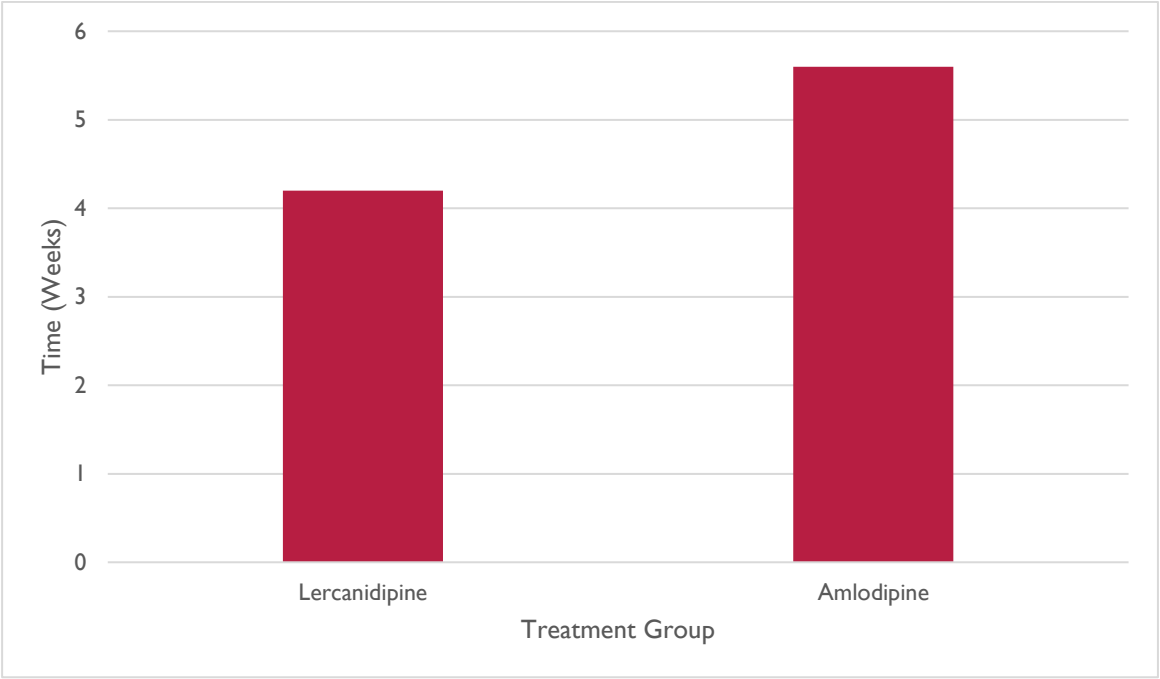


Figure 2: Adherence Rates (%)

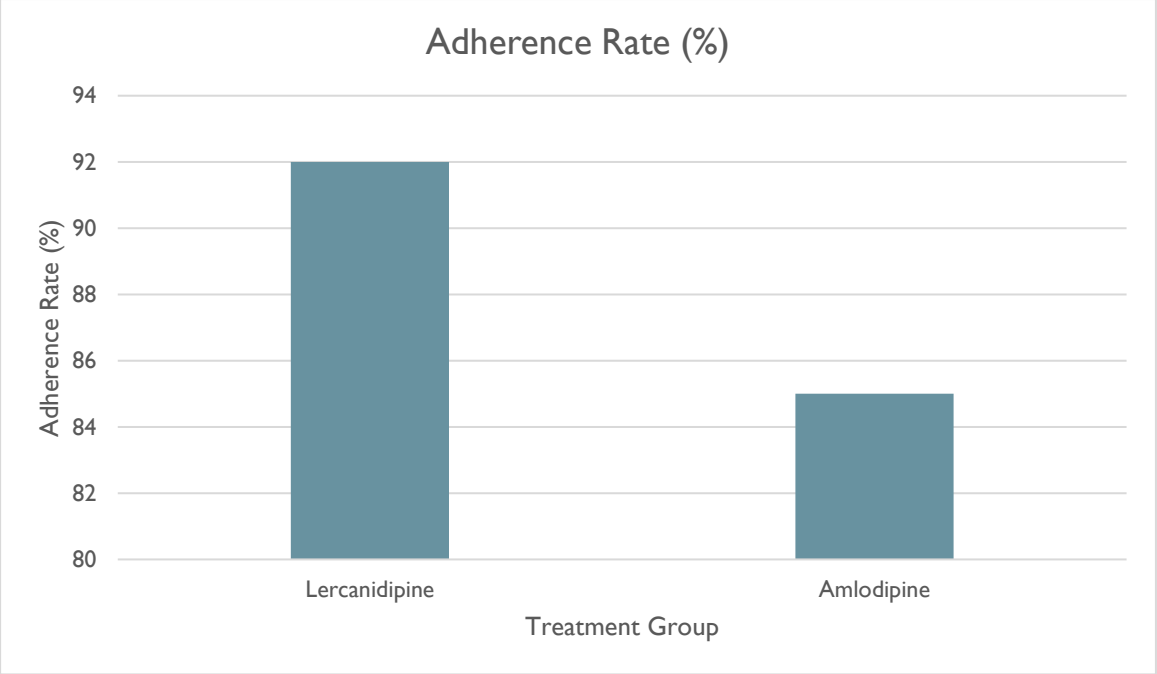


Figure 3: Incidence of Peripheral Edema (%)

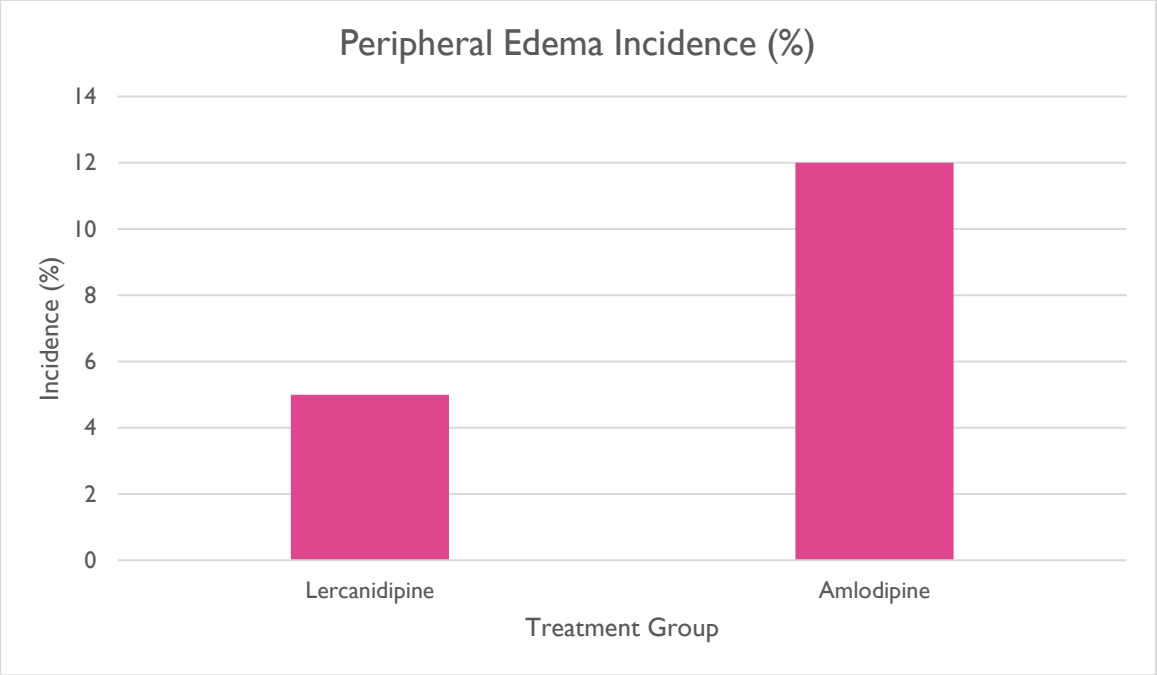


Figure 4: Alpha Diversity of Gut Microbiota (Shannon Index)

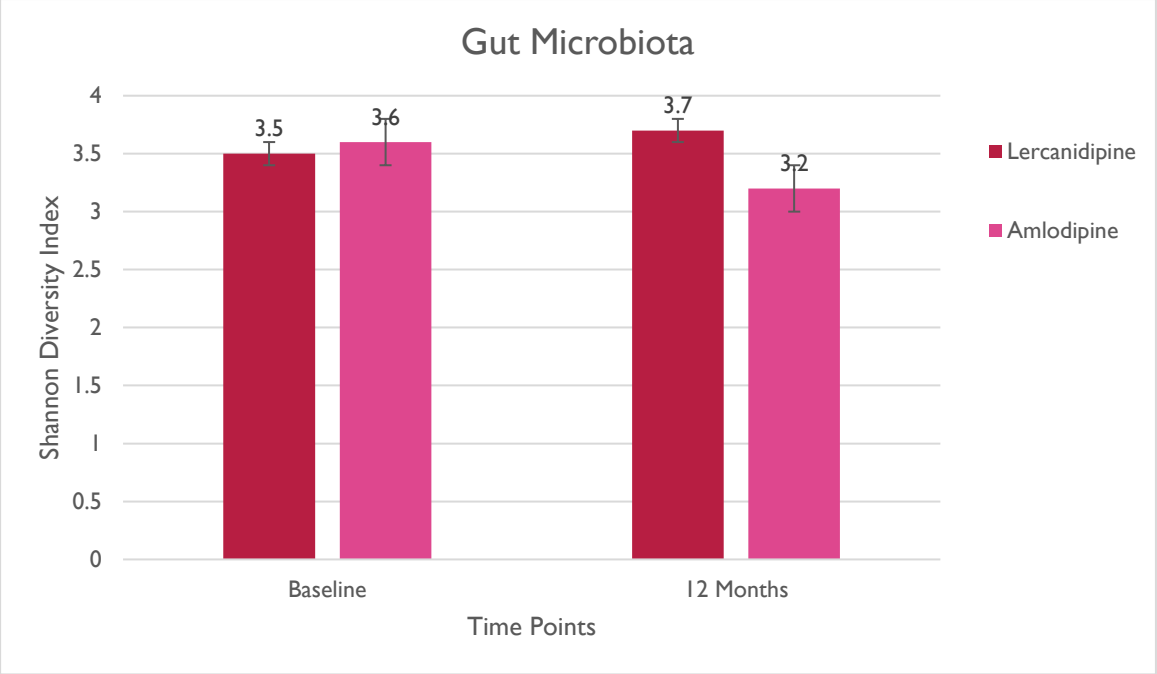


Figure 5: Beta Diversity Analysis of Gut Microbiota (PCoA Plot using Bray-Curtis Dissimilarity)

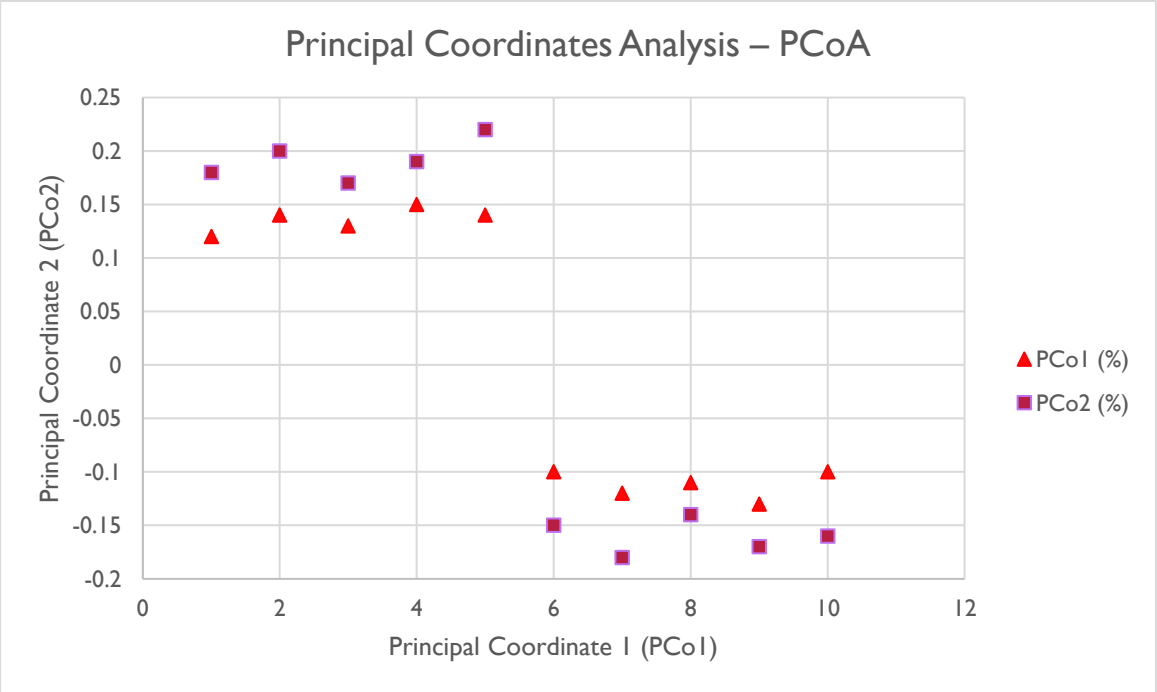


Figure 6: Relative Abundance of Major Bacterial Phyla at 12 Months

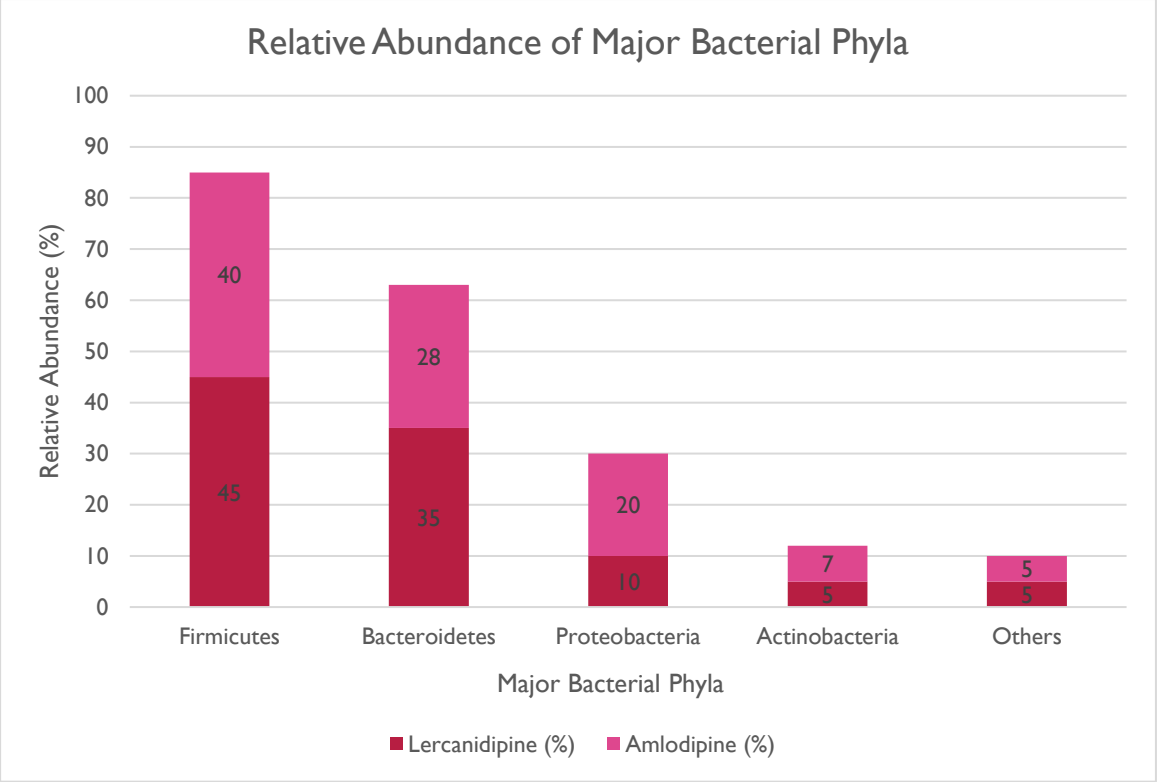
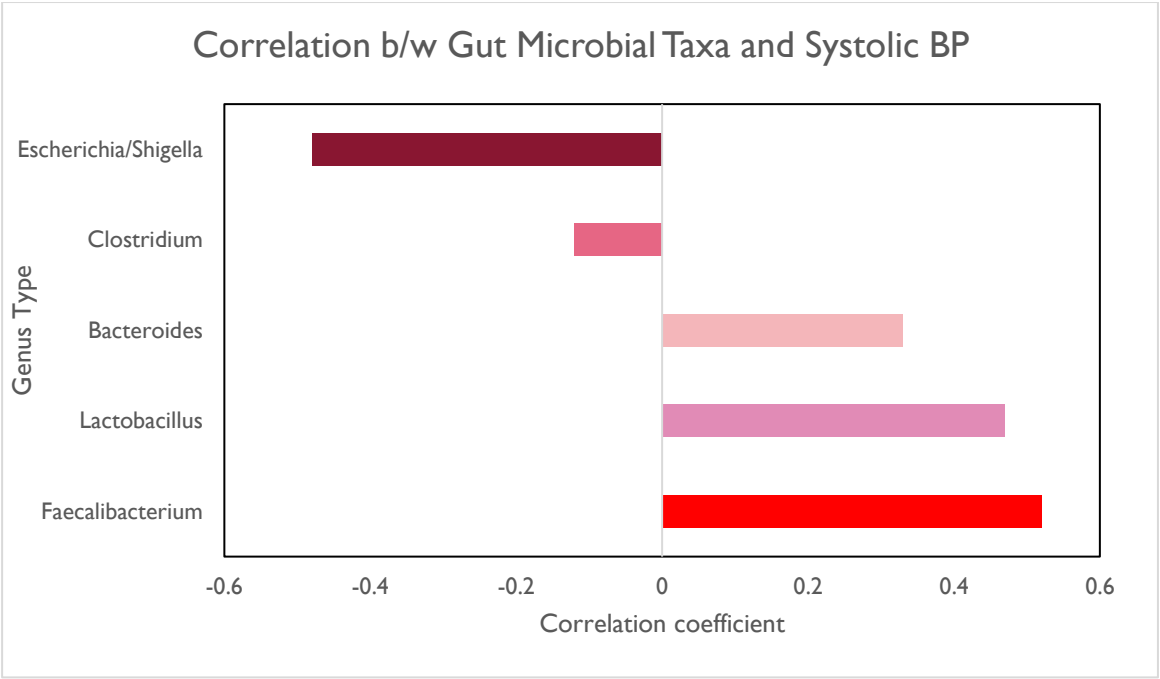


Figure 7: Heatmap of Differentially Abundant Gut Microbial Taxa (Genus Level)

Genus	Lercanidipine (%)	Amlodipine (%)
Lactobacillus	4.5	2.1
Bacteroides	10.2	8.4
Escherichia/Shigella	2	6.8
Faecalibacterium	5.8	3.2
Prevotella	3.5	3
Clostridium	6	5.7

Figure 8: Correlation Between Gut Microbial Taxa and Systolic Blood Pressure Reduction



4. DISCUSSION

The findings of this study reaffirm the comparable efficacy of lercanidipine and amlodipine in reducing systolic and diastolic blood pressure in patients with essential hypertension [20]. While both calcium channel blockers significantly improved blood pressure control over 12 months, lercanidipine demonstrated a faster time to achieve target values, a trend consistent with previous comparative studies [21]. One of the major advantages observed with lercanidipine was its improved tolerability profile, notably a reduced incidence of peripheral edema and vasodilatory side effects, which has also been supported in recent multicenter trials [22]. This tolerability likely enhances patient adherence, a critical factor in long-term hypertension management [23].

Emerging literature has emphasized the intricate role of the gut microbiota in modulating cardiovascular physiology, including blood pressure regulation via metabolites such as short-chain fatty acids and trimethylamine-N-oxide [24]. In our study, lercanidipine was associated with a preservation of microbial diversity and a shift toward anti-inflammatory taxa, while amlodipine was linked to a mild decrease in alpha diversity and enrichment of pro-inflammatory genera. These findings echo earlier reports suggesting drug-specific modulation of gut microbial communities, which may partially explain inter-individual differences in drug response [25,26]. The microbial shifts observed in the lercanidipine group align with beneficial cardiovascular effects, such as reduced systemic inflammation and improved endothelial function [27].

These results highlight the potential of gut microbiota as both a biomarker and a therapeutic target in hypertension. The interaction between antihypertensive agents and gut microbiota composition has been increasingly recognized as a contributor to variability in drug efficacy and adverse event profiles [28,29]. Recent mechanistic studies suggest that calcium channel blockers may affect microbial enzymes involved in bile acid metabolism, impacting host metabolic pathways [30]. The clinical relevance of this microbiota-drug interaction is underscored by the growing body of evidence linking microbial dysbiosis to poor cardiovascular outcomes [31].

While the study adds novel insights into pharmacomicrobiomics in hypertension, it is not without limitations. The open-label design introduces potential biases, and gut microbiota assessment was limited to 16S rRNA sequencing, which provides taxonomic resolution but limited functional inference [32]. Furthermore, the study was geographically confined, which may limit generalizability due to regional dietary and microbiota variations [33]. Despite these constraints, the longitudinal design and integration of clinical and microbiome data strengthen the findings.

Future directions should include metagenomic or metabolomic analyses to explore the functional implications of microbiota shifts and their causal roles in modulating drug responses [34]. Larger, multicentric trials with ethnically and demographically diverse populations are also essential to validate these findings [35]. In parallel, preclinical models may offer mechanistic insights into how specific microbial taxa influence calcium channel blocker metabolism [36]. Ultimately, incorporating gut microbiota profiles into routine clinical algorithms may pave the way for microbiome-informed personalized therapy in hypertension [37].

5. CONCLUSION

This study demonstrates that both lercanidipine and amlodipine are effective in achieving blood pressure control in patients with essential hypertension; however, lercanidipine offers superior tolerability and a faster time to reach target blood pressure levels. Importantly, lercanidipine was also associated with a more favorable modulation of gut microbiota, maintaining microbial diversity and enriching cardioprotective taxa, unlike amlodipine, which showed signs of microbiota perturbation. These findings highlight not only the clinical benefits of lercanidipine in terms of efficacy and patient adherence but also underscore the emerging relevance of gut microbiota as a determinant of drug response in hypertension. Integrating microbiome profiles into antihypertensive treatment strategies may enable a more personalized, holistic approach to managing cardiovascular risk

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