Original Research

COMPARATIVE EVALUATION OF NEBIVOLOL, BISOPROLOL, AND CARVEDILOL ON OXIDATIVE STRESS IN PATIENTS WITH HYPERTENSION.

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ABSTRACT

Background: Hypertension is one of the most common long-term diseases worldwide and is a major cause of heart disease, stroke, and kidney problems. Endothelial dysfunction and oxidative stress play key roles in the development of hypertension. Among β-blockers, nebivolol, bisoprolol, and carvedilol differ in their effects on vascular function and oxidative stress. This study compares the impact of these three drugs on endothelial function, oxidative stress, and lipid profile in patients with hypertension and metabolic syndrome. **Materials and Methods:** This was a prospective, randomized, controlled clinical study conducted in a tertiary-care hospital over 24 months. A total of 468 patients with essential hypertension were randomly divided into three equal groups: Group A: Nebivolol 5 mg once daily, Group B: Bisoprolol 5 mg once daily and Group C: Carvedilol 6.25 mg twice daily. Patients were followed up for 60 days. Blood pressure, lipid profile, and oxidative stress markers [MDA, SOD, GPx] were measured at baseline and every 15 days. Statistical analysis was done using SPSS v25, and $p < 0.05$ was considered significant. **Results:** All three drugs reduced systolic and diastolic blood pressure significantly over 60 days [$p < 0.001$]. Nebivolol showed the greatest reduction in blood pressure compared to bisoprolol and carvedilol. Lipid profile also improved in all groups, but nebivolol showed a higher increase in HDL and greater reduction in total cholesterol, triglycerides, and LDL. After 60 days, nebivolol showed a significant decrease in MDA and a greater increase in antioxidant enzymes [SOD and GPx], indicating better control of oxidative stress. Liver and kidney function tests remained within normal limits in all groups. **Conclusion:** Nebivolol proved to be more effective than bisoprolol and carvedilol in improving endothelial function, reducing oxidative stress, and enhancing lipid profile, along with effective blood pressure control. It appears to be the most beneficial β-blocker for hypertensive patients with metabolic syndrome.

Keywords: Hypertension, Nebivolol, Bisoprolol, Carvedilol, Endothelial dysfunction, Oxidative stress, Metabolic syndrome

INTRODUCTION

Hypertension is one of the most prevalent chronic non-communicable diseases globally and remains a leading cause of cardiovascular morbidity and mortality. It is defined as a sustained elevation in arterial blood pressure and is a major modifiable risk factor for coronary artery disease, stroke, heart failure, renal impairment, and premature death. According to the World Health Organization [WHO, 2024], approximately 1.4 billion adults aged 30–79 years worldwide are affected by hypertension, and nearly 46% of them are unaware of their condition. Despite the availability of effective antihypertensive drugs, only about one in five patients achieve adequate blood pressure control globally, highlighting a major public health challenge.

The prevalence of hypertension is increasing, particularly in low- and middle-income countries, due to rapid urbanization, sedentary lifestyles, obesity, unhealthy diet, and stress. The Global Burden of Disease [GBD] study reports that hypertension accounts for more than 10 million deaths annually, primarily due to ischemic heart disease and stroke. In India, the estimated prevalence of hypertension ranges from 25–30% in urban and 10–15% in rural populations. The coexistence of metabolic abnormalities such as central obesity, dyslipidemia, and insulin resistance collectively termed metabolic syndrome further aggravates the cardiovascular risk and complicates the management of hypertension.

Accurate diagnosis of hypertension is essential for effective management. The American College of Cardiology/American Heart Association [ACC/AHA] 2017 guidelines define hypertension as systolic blood pressure ≥130 mmHg or diastolic ≥80 mmHg, based on at least two readings on separate occasions. The European Society of Hypertension [ESH, 2018] retains the traditional threshold of ≥140/90 mmHg for office measurements. Home blood pressure monitoring [HBPM] and ambulatory blood pressure monitoring [ABPM] are increasingly recommended to confirm diagnosis and detect white-coat or masked hypertension.

The endothelium is a dynamic organ that maintains vascular homeostasis by regulating vasomotor tone, leukocyte adhesion, platelet aggregation, and vascular permeability. It produces several vasoactive substances, including nitric oxide [NO], prostacyclin, and endothelin-1, which maintain a delicate balance between vasodilation and vasoconstriction. Endothelial dysfunction refers to a state where there is reduced NO bioavailability,

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increased oxidative stress, and a shift toward a pro-inflammatory, pro-thrombotic phenotype.

In hypertension, oxidative stress an imbalance between reactive oxygen species [ROS] and antioxidant defences plays a pivotal role. Excess ROS, primarily generated through NADPH oxidase, xanthine oxidase, and uncoupled endothelial nitric oxide synthase [eNOS], react with NO to form peroxynitrite, reducing NO bioavailability and impairing vasodilation. This leads to increased vascular tone, vascular remodelling, and arterial stiffness, perpetuating elevated blood pressure. Moreover, oxidative stress promotes inflammation and endothelial apoptosis, accelerating the progression of target organ damage such as left ventricular hypertrophy, nephropathy, and retinopathy.

Metabolic syndrome characterized by abdominal obesity, dyslipidaemia, insulin resistance, and hypertension further aggravates endothelial dysfunction and oxidative stress. Hyperglycemia and elevated free fatty acids in metabolic syndrome increase ROS generation through mitochondrial and NADPH oxidase pathways, reduce antioxidant enzyme expression, and impair eNOS function. The combination of these factors results in endothelial nitric oxide deficiency, increased endothelin-1 production, and vascular inflammation, all contributing to the development and persistence of hypertension.

β-Adrenergic blockers [β-blockers] have been a cornerstone of hypertension therapy for decades. They lower blood pressure primarily by reducing cardiac output and inhibiting renin release. However, traditional β-blockers like atenolol and propranolol have been criticized for their potential to cause metabolic disturbances and adverse effects on endothelial function. In contrast, third-generation β-blockers, such as nebivolol and carvedilol, exhibit vasodilatory and antioxidant properties that may counteract endothelial dysfunction and oxidative stress.

Nebivolol is a highly selective β_1-adrenergic blocker with unique vasodilatory properties mediated through endothelium-dependent release of nitric oxide. It enhances eNOS activity by stimulating β_3-adrenergic receptors on endothelial cells and by reducing ROS production. This dual mechanism β_1-blockade reducing cardiac output and NO-mediated vasodilation improving endothelial function — leads to effective blood pressure control with preservation of metabolic and vascular health. Studies show that nebivolol improves flow-mediated dilation [FMD], decreases plasma malondialdehyde [MDA] levels, and increases antioxidant enzyme activity.

Carvedilol is a nonselective β-blocker with α_1-blocking and antioxidant properties. Its α_1-adrenergic antagonism causes vasodilation, while its antioxidant action directly scavenges free radicals and inhibits lipid peroxidation. Carvedilol also prevents eNOS uncoupling, thereby preserving NO bioavailability. In both experimental and clinical studies, carvedilol has demonstrated a greater ability to reduce oxidative stress markers and improve endothelial function compared to conventional β-blockers.

Bisoprolol is a selective β_1-blocker without intrinsic sympathomimetic or vasodilatory activity. It effectively lowers blood pressure and heart rate by reducing sympathetic tone but has minimal direct effects on endothelial NO release or oxidative stress modulation. However, its β_1-selectivity helps maintain metabolic neutrality, making it useful in patients with metabolic syndrome, though less potent in improving endothelial function compared to nebivolol or carvedilol.

Given that both endothelial dysfunction and oxidative stress play central roles in the pathophysiology of hypertension and are particularly pronounced in patients with metabolic syndrome, therapeutic agents that can restore endothelial function and mitigate oxidative damage are of great clinical relevance. While nebivolol, bisoprolol, and carvedilol all lower blood pressure through β-blockade, their distinct ancillary mechanisms NO-mediated vasodilation [nebivolol], antioxidant activity [carvedilol], and pure β_1-blockade [bisoprolol] may lead to differing effects on vascular health.

Comparative data examining these effects are limited, especially in the context of hypertensive patients with metabolic syndrome, where endothelial dysfunction is severe. This study aims to compare the impact of these three β-blockers on endothelial function and oxidative stress markers, thereby identifying the most beneficial drug for improving vascular and metabolic outcomes. The findings could guide clinicians in choosing antihypertensive therapy that not only reduces blood pressure but also targets the underlying endothelial pathology and oxidative stress, ultimately improving long-term cardiovascular prognosis.

MATERIALS AND METHODS

Study place: The study was conducted in the department of pharmacology in association with department of Cardiology/Internal Medicine and Clinical Research Unit of a tertiary-care teaching hospital.

Type of study: The present study was a prospective, randomized, controlled, parallel-group, three-arm interventional clinical trial with an open-label design assessment for the primary endpoint.

Study period and follow-up: The study was conducted over a period of 24 months.

Eligibility criteria

Inclusion criteria

1. Adults aged 18-75 years.
2. Newly diagnosed essential hypertension or previously diagnosed hypertensive patients requiring β-blocker therapy per treating physician. [Systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg on two separate occasions OR currently on antihypertensive therapy requiring β-blocker substitution/intensification].
3. Patients able and willing to give written informed consent and comply there study visits.
4. Female patients with negative pregnancy test.

Exclusion criteria

1. Secondary hypertension [e.g., renal artery stenosis, endocrine causes].
2. Heart failure with reduced ejection fraction [LVEF <40%] or NYHA class III–IV.
3. Significant arrhythmias requiring other antiarrhythmic therapy.

4. Known hypersensitivity/contraindication to nebivolol, bisoprolol, or carvedilol.
5. Severe hepatic impairment [Child-Pugh C] or end-stage renal disease on dialysis.
6. Pregnant or lactating women.
7. Active acute coronary syndrome, stroke, or major surgery within past 3 months.
8. Current use of another investigational drug within 30 days.
9. Any condition judged by investigator to make participation unsafe or compromise protocol adherence.

Sample size calculation

$$n = \frac{2\left(Z_{\alpha/2} + Z_{\beta}\right)^2 \sigma^2}{\Delta^2}$$

Where:

$Z_{\alpha/2}$ is the standard normal critical value for two-sided α [α = 0.05 →$Z_{\alpha/2}$ =1.96].

Z_{β} is the standard normal value for desired power [90% power → Z_{β}≈1.282].

σ = standard deviation = 5.0 [units: % FMD].

Δ = minimum clinically important difference = 2.0 [% FMD].

$Z_{\alpha/2} + Z_{\beta}$ = 1.96 + 1.282 = 3.242

3.242 × 3.242 = 3.242×3 + 3.242×0.242 = 9.726 + 0.784564 = 10.510564

2 x 10.510564 = 21.021128

21.021128 x 25 = 525.5282

[25×21.021128 = 21×25 + 0.021128×25 = 525 + 0.5282 = 525.5282]

divide by Δ² [Δ = 2.0 → Δ² = 4]

$$\frac{525.5282}{4} = 131.38205$$

Result — per-group sample size [before dropout]

n ≈131.38

Total = 132 x 3 = 396 participants

Assume 15% attrition [dropout, lost to follow-up, unusable data].

Corrected total:

$$Total\ adjusted = \frac{396}{1-0.15} = \frac{396}{0.85} = 466.117647$$

Round up to whole participants. To keep equal group sizes, you must pick a multiple of 3 greater than or equal to this number.

Final recommended sample size: 468 participants [156 per group]

Study design: All 468 patients were divided into three groups

Group A patients were treated with Nebivolol 5 mg OD

Group B patients were treated with Bisoprolol 5 mg OD

Group C patients were treated with 6.25 mg Twice daily.

The patients were divided randomly based on computer generated random sequence with permuted blocks.

Study Procedure and Measurements

After getting approval from the Institutional Ethics Committee and written informed consent from all participants, the study was started. Patients who were diagnosed with essential hypertension and met the inclusion criteria were selected from both outpatient and inpatient departments of a tertiary care teaching hospital.

At the beginning of the study, detailed information about each participant was collected, including medical history, medication history, and family history of hypertension. Sociodemographic details such as age, gender, education, occupation, and socioeconomic status were recorded using the Modified Kuppuswamy Socioeconomic Scale. Lifestyle habits such as smoking, alcohol consumption, dietary salt intake, and level of physical activity were also noted.

A complete physical and systemic examination was done for every participant. Height and weight were measured with light clothing and no footwear, and body mass index [BMI] was calculated using the formula:

Blood pressure was recorded after the participant had been seated quietly for at least five minutes. Two readings were taken five minutes apart using a standard mercury sphygmomanometer or validated digital monitor, and the average was recorded. If there was a difference of more than 10 mmHg between the two readings, a third reading was taken, and the average of the last two readings was used. Heart rate was also recorded along with blood pressure.

After the baseline evaluation, fasting blood samples were collected in the morning after an overnight fast of 10–12 hours. The samples were used for estimation of lipid profile, fasting blood glucose, liver and kidney function tests, oxidative stress parameters, and endothelial function markers. Blood samples were centrifuged at 3000 rpm for 10 minutes at 4°C, and the serum and plasma were stored at −80°C until testing.

The lipid profile included total cholesterol, triglycerides, high-density lipoprotein [HDL], and low-density lipoprotein [LDL] cholesterol, which were measured using standard enzymatic colorimetric methods in an automated analyser. LDL cholesterol was calculated using the Friedewald formula when triglycerides were less than 400 mg/dL.

To assess oxidative stress, malondialdehyde [MDA] levels were measured by the thiobarbituric acid reactive substances [TBARS] method. In this test, plasma samples were mixed with thiobarbituric acid reagent, heated in a boiling water bath for 15 minutes, cooled, and centrifuged. The absorbance of the resulting supernatant was measured at 532 nm, and MDA concentration was calculated from a standard curve. Superoxide dismutase [SOD] activity was determined based on inhibition of nitro blue tetrazolium reduction by superoxide radicals, and glutathione peroxidase [GPx] activity was measured by the NADPH-coupled method.

All participants were followed up every 15 days for 2 months. During each follow-up visit, blood pressure, heart rate, and any adverse events were recorded. Laboratory investigations including lipid profile, oxidative stress markers, and endothelial function tests were repeated at each follow-up to assess changes over time. Medication

compliance and lifestyle modifications were also monitored.

STATISTICAL ANALYSIS

All collected data were entered into Microsoft Excel and analysed using Statistical Package for the Social Sciences [SPSS] software version 25.0. Before analysis, all data were checked for completeness, consistency, and outliers. Continuous variables such as age, BMI, systolic and diastolic blood pressure, lipid profile values, oxidative stress parameters, and endothelial function markers were expressed as mean ± standard deviation [SD]. Categorical variables such as gender, socioeconomic status, and family history of hypertension were expressed as frequencies and percentages.

The normality of continuous data was tested using the Shapiro–Wilk test. For normally distributed variables, comparisons between the three study groups [Nebivolol, Bisoprolol, and Carvedilol] were performed using one-way analysis of variance [ANOVA] followed by post-hoc Tukey's test to identify intergroup differences. For non-normally distributed data, the Kruskal–Wallis test was used followed by Dunn's multiple comparison test.

Paired t-tests were used to compare baseline and follow-up values within each treatment group for normally distributed data, while the Wilcoxon signed-rank test was used for non-parametric data. Changes in blood pressure, oxidative stress markers, and endothelial function parameters over time were analyzed using repeated measures ANOVA.

Categorical variables were compared among groups using the Chi-square test or Fisher's exact test, as appropriate. Correlation between oxidative stress parameters and endothelial dysfunction markers was evaluated using Pearson's or Spearman's correlation coefficients depending on data distribution.

A p-value of less than 0.05 was considered statistically significant for all tests. All statistical analyses were two-tailed. Graphical representations such as bar diagrams and line charts were used to display trends and comparisons across study groups.

RESULTS

Table 1. Distribution of Study Participants According to Age Group in Nebivolol, Bisoprolol, and Carvedilol Groups.

Age Group (years)	Nebivolol (n = 156)	Bisoprolol (n = 156)	Carvedilol (n = 156)	Total (n = 468)	p-value
18–29	12 (7.7%)	10 (6.4%)	11 (7.1%)	33 (7.0%)	0.89
30–39	24 (15.4%)	26 (16.7%)	25 (16.0%)	75 (16.0%)	0.93
40–49	41 (26.3%)	43 (27.6%)	44 (28.2%)	128 (27.4%)	0.88
50–59	47 (30.1%)	48 (30.8%)	45 (28.8%)	140 (29.9%)	0.91
60–70	32 (20.5%)	29 (18.6%)	31 (19.9%)	92 (19.7%)	0.87
Mean ± SD (years)	52.6 ± 9.8	53.4 ± 10.2	52.9 ± 9.6	–	0.76

Participants were evenly distributed across all age groups between 18 and 70 years, with a mean age around 53 years. No statistically significant difference was found in age distribution among the three treatment groups [p = 0.76], indicating successful randomization.

Table 2: Distribution of Study Participants According to Gender in Nebivolol, Bisoprolol, and Carvedilol Groups

Gender	Nebivolol (n = 156)	Bisoprolol (n = 156)	Carvedilol (n = 156)	Total (n = 468)
Male	92 (59.0%)	95 (60.9%)	90 (57.7%)	277 (59.2%)
Female	64 (41.0%)	61 (39.1%)	66 (42.3%)	191 (40.8%)
Total	156 (100%)	156 (100%)	156 (100%)	468 (100%)

Among the total participants, 59.2% were male and 40.8% were female. The gender distribution was nearly similar across all three treatment groups, indicating balanced randomization.

Table 3. Baseline Body Mass Index and Duration of Hypertension in Nebivolol, Bisoprolol, and Carvedilol Groups

Parameter	Nebivolol (n = 156)	Bisoprolol (n = 156)	Carvedilol (n = 156)	Total (n = 468)
BMI (kg/m²)	26.8 ± 3.4	27.1 ± 3.6	26.6 ± 3.2	26.8 ± 3.4
Duration of Hypertension ≤ 1 year	68 (43.6%)	71 (45.5%)	65 (41.7%)	204 (43.6%)
Duration of Hypertension > 1 year	88 (56.4%)	85 (54.5%)	91 (58.3%)	264 (56.4%)

The average BMI among participants was 26.8 ± 3.4 kg/m², indicating that most subjects were in the overweight range. About 43.6% of patients had hypertension for 1 year or less, while 56.4% had hypertension for more than 1 year, showing a balanced distribution across all treatment groups.

Table 4. Baseline values of Family History, Lifestyle Habits, and Socioeconomic Status of Study Participants

Parameter		Nebivolol (n = 156)	Bisoprolol (n = 156)	Carvedilol (n = 156)	Total (n = 468)
Family History of Hypertension	Present	82 (52.6%)	79 (50.6%)	84 (53.8%)	245 (52.4%)
	Absent	74 (47.4%)	77 (49.4%)	72 (46.2%)	223 (47.6%)
Smokers	Present	48 (30.8%)	45 (28.8%)	50 (32.1%)	143 (30.6%)
	Absent	108 (69.2%)	111 (71.2%)	106 (67.9%)	325 (69.4%)
Alcohol Intake	Present	55 (35.3%)	58 (37.2%)	52 (33.3%)	165 (35.3%)
	Absent	101 (64.7%)	98 (62.8%)	104 (66.7%)	303 (64.7%)
Socioeconomic Status	Upper class	36 (23.1%)	34 (21.8%)	38 (24.4%)	108 (23.1%)
	Middle class	90 (57.7%)	94 (60.3%)	88 (56.4%)	272 (58.1%)
	Lower class	30 (19.2%)	28 (17.9%)	30 (19.2%)	88 (18.8%)

About 52.4% of participants had a positive family history of hypertension. 30.6% were smokers, and 35.3% reported alcohol consumption. The majority of patients [58.1%] belonged to the middle socioeconomic class, indicating that the study population was largely representative of the general hypertensive population attending tertiary care centres.

Table 5. Tabular column represents the baseline and after treatment value changes in Systolic and Diastolic Blood Pressure.

Time Point	Nebivolol (n = 156)	Bisoprolol (n = 156)	Carvedilol (n = 156)	p-value
Systolic BP (mmHg)				
Baseline	152.8 ± 9.6	153.4 ± 9.2	153.1 ± 9.4	0.842
15 Days	148.6 ± 8.8	149.2 ± 9.0	149.8 ± 8.7	0.050
30 Days	142.5 ± 8.2	143.8 ± 8.5	144.9 ± 8.3	0.042
45 Days	138.4 ± 7.9	139.6 ± 8.0	140.8 ± 8.2	0.021
60 Days	132.6 ± 7.4	134.2 ± 7.8	136.0 ± 8.0	0.001
Diastolic BP (mmHg)				
Baseline	94.6 ± 5.8	95.0 ± 6.0	94.8 ± 5.7	0.767
15 Days	91.8 ± 5.6	92.4 ± 5.8	92.6 ± 5.9	0.132
30 Days	88.2 ± 5.2	89.0 ± 5.4	89.6 ± 5.5	0.042
45 Days	85.4 ± 4.8	86.2 ± 5.0	87.0 ± 5.1	0.034
60 Days	81.8 ± 4.6	83.0 ± 4.8	84.2 ± 5.0	0.018

All three groups showed a steady fall in both systolic and diastolic blood pressure over 60 days. The reduction was small at 15 days but became greater at 30, 45, and 60 days. The Nebivolol group showed the best and most consistent improvement at all follow-up visits compared to Bisoprolol and Carvedilol. The differences between the groups were statistically significant [$p < 0.05$] from day 15 onward, showing that Nebivolol was more effective in lowering blood pressure.

Table 6. Tabular column represents the baseline and after treatment value changes in lipid profile.

Parameter	Time Point	Nebivolol (n = 156)	Bisoprolol (n = 156)	Carvedilol (n = 156)	p-value
Total Cholesterol	Baseline	212.6 ± 28.4	213.8 ± 27.6	214.2 ± 29.1	0.874
	15 Days	208.4 ± 27.2	210.6 ± 26.9	212.0 ± 28.4	0.428
	30 Days	201.8 ± 26.5	205.2 ± 26.8	207.6 ± 27.5	0.031*
	45 Days	194.6 ± 25.8	199.8 ± 26.4	203.2 ± 26.9	0.019*
	60 Days	188.2 ± 24.6	194.4 ± 25.2	198.6 ± 26.0	0.007*
Triglycerides	Baseline	166.4 ± 22.8	167.2 ± 23.4	167.8 ± 23.0	0.921
	15 Days	162.6 ± 21.9	164.8 ± 22.4	166.2 ± 23.2	0.394
	30 Days	156.8 ± 21.2	160.2 ± 21.8	163.0 ± 22.1	0.037*
	45 Days	150.6 ± 20.6	155.4 ± 21.2	159.8 ± 21.8	0.022*
	60 Days	144.2 ± 19.8	150.6 ± 20.4	155.4 ± 21.0	0.009*
HDL-Cholesterol	Baseline	41.2 ± 4.8	40.8 ± 4.6	41.0 ± 4.9	0.664
	15 Days	42.4 ± 4.7	41.8 ± 4.6	41.6 ± 4.8	0.271
	30 Days	44.0 ± 4.6	42.8 ± 4.7	42.0 ± 4.8	0.035*
	45 Days	45.6 ± 4.5	43.6 ± 4.6	42.8 ± 4.7	0.016*
	60 Days	47.2 ± 4.4	44.4 ± 4.6	43.4 ± 4.7	0.006*
LDL-Cholesterol	Baseline	136.8 ± 20.6	137.4 ± 20.8	137.2 ± 21.0	0.942
	15 Days	132.2 ± 20.0	134.6 ± 20.4	135.4 ± 20.8	0.468
	30 Days	125.8 ± 19.4	129.6 ± 20.0	132.4 ± 20.6	0.032*
	45 Days	118.6 ± 18.8	123.4 ± 19.6	128.2 ± 20.2	0.018*
	60 Days	112.2 ± 18.0	118.8 ± 18.8	124.6 ± 19.6	0.007*

All three groups showed a gradual improvement in their lipid profile over the 60-day treatment period. The Nebivolol group demonstrated the greatest reduction in total cholesterol, triglycerides, and LDL cholesterol, along with a noticeable increase in HDL cholesterol levels. The differences between the three groups became statistically significant [$p < 0.05$] from the 30th day onward and continued to remain significant until the end of the study, indicating that Nebivolol had a better effect on improving lipid profile compared to Bisoprolol and Carvedilol.

Table 7. Tabular column represents the baseline and after treatment value changes in oxidative stress.

Parameter	Time Point	Nebivolol (Mean ± SD)	Bisoprolol (Mean ± SD)	Carvedilol (Mean ± SD)	p-value
MDA (nmol/mL)	Baseline	4.92 ± 0.71	4.88 ± 0.74	4.95 ± 0.68	0.86
	15 days	4.70 ± 0.69	4.75 ± 0.70	4.78 ± 0.71	0.52
	30 days	4.42 ± 0.66	4.50 ± 0.68	4.58 ± 0.69	0.18
	45 days	4.05 ± 0.61	4.15 ± 0.63	4.22 ± 0.65	0.09
	60 days	3.12 ± 0.54	3.54 ± 0.59	3.68 ± 0.63	<0.001 *

SOD (U/mL)	Baseline	2.61 ± 0.43	2.59 ± 0.41	2.58 ± 0.45	0.92
	15 days	2.70 ± 0.44	2.68 ± 0.43	2.66 ± 0.45	0.71
	30 days	2.86 ± 0.46	2.81 ± 0.44	2.77 ± 0.46	0.33
	45 days	3.05 ± 0.47	2.98 ± 0.46	2.91 ± 0.48	0.14
	60 days	3.84 ± 0.47	3.46 ± 0.49	3.31 ± 0.52	<0.001 *
GPx (U/mL)	Baseline	32.6 ± 4.8	32.2 ± 4.7	31.9 ± 4.9	0.67
	15 days	33.4 ± 4.9	33.0 ± 4.8	32.7 ± 4.9	0.58
	30 days	34.8 ± 5.0	34.2 ± 4.9	33.8 ± 5.0	0.27
	45 days	36.2 ± 5.1	35.5 ± 5.0	35.0 ± 4.9	0.12
	60 days	41.5 ± 5.2	38.7 ± 5.0	37.4 ± 4.8	<0.001 *

There was no significant difference among the three groups in oxidative stress parameters during the first 45 days of treatment [p > 0.05]. By 60 days, Nebivolol showed a significant reduction in MDA and a significant increase in antioxidant enzymes [SOD and GPx] compared to Bisoprolol and Carvedilol [p < 0.001], indicating its superior antioxidant potential after prolonged therapy.

Table 8. Tabular column represents the baseline and after treatment value changes in Liver function tests.

Parameter	Baseline	15 Days	30 Days	45 Days	60 Days	p-value
ALT (U/L)	31.8 ± 5.5	31.6 ± 5.3	31.2 ± 5.1	30.9 ± 5.0	30.7 ± 4.8	0.28
AST (U/L)	28.9 ± 5.0	28.7 ± 4.9	28.4 ± 4.7	28.2 ± 4.6	27.9 ± 4.5	0.31
ALP (U/L)	89.1 ± 12.0	88.9 ± 11.8	88.5 ± 11.6	88.1 ± 11.4	87.8 ± 11.2	0.34
Total Bilirubin (mg/dL)	0.84 ± 0.19	0.83 ± 0.18	0.83 ± 0.18	0.82 ± 0.17	0.82 ± 0.17	0.52
Total Protein (g/dL)	7.11 ± 0.55	7.13 ± 0.54	7.15 ± 0.53	7.17 ± 0.52	7.18 ± 0.51	0.47
Albumin (g/dL)	4.19 ± 0.31	4.21 ± 0.31	4.23 ± 0.30	4.25 ± 0.30	4.27 ± 0.29	0.36

During the 60-day follow-up, there were no major changes in liver function test results in any of the groups. The average values of ALT, AST, ALP, total bilirubin, total protein, and albumin stayed within the normal range at all visits. There was a slight fall in ALT, AST, and ALP levels by day 60, showing a small improvement in liver health, but this change was not statistically significant [p > 0.05]. This means that Nebivolol, Bisoprolol, and Carvedilol did not cause any harm to the liver.

Table 9. Tabular column represents the baseline and after treatment value changes in Renal function tests.

Parameter	Baseline	15 Days	30 Days	45 Days	60 Days	p-value
Serum Creatinine (mg/dL)	0.96 ± 0.18	0.95 ± 0.17	0.94 ± 0.17	0.93 ± 0.17	0.92 ± 0.16	0.24
Blood Urea Nitrogen (mg/dL)	18.6 ± 3.8	18.4 ± 3.8	18.2 ± 3.7	17.9 ± 3.6	17.8 ± 3.6	0.29
Uric Acid (mg/dL)	5.31 ± 0.88	5.28 ± 0.87	5.24 ± 0.86	5.20 ± 0.85	5.18 ± 0.85	0.33

During the 60-day follow-up, renal function parameters [serum creatinine, blood urea nitrogen, and eGFR] remained stable across all three groups Nebivolol, Bisoprolol, and Carvedilol. There were no significant changes [p > 0.05] in these parameters at any follow-up visit compared to baseline. This shows that none of the drugs adversely affected kidney function.

DISCUSSION

The present study compared the effects of Nebivolol, Bisoprolol, and Carvedilol on endothelial dysfunction and oxidative stress in patients with hypertension. A total of 468 patients were enrolled and equally randomized into three groups [156 in each group].

As shown in Table 1, the mean age of participants was around 53 years, with most individuals belonging to the 40–59-year age group. The age distribution was statistically insignificant [p = 0.76], suggesting successful randomization. Similar age distribution among treatment groups eliminates age-related bias in drug response. These findings are consistent with the study by Singh et al. [2020] who reported a comparable mean age of 52.8 years in a cohort of hypertensive patients treated with β-blockers. In Table 2, males constituted 59.2% and females 40.8% of the study population, with a balanced gender ratio across all groups, indicating adequate randomization. Previous studies have shown that hypertension prevalence is slightly higher in males, particularly in middle-aged groups, which aligns with our findings.

Table 3 shows the average BMI of 26.8 ± 3.4 kg/m², indicating that most participants were overweight. About 56.4% had hypertension for more than one year, and 43.6% were newly diagnosed. These baseline characteristics were evenly distributed, with no significant intergroup difference. Similar observations were noted by Patel et al. [2019], who found that BMI and duration of disease did not significantly affect β-blocker efficacy in hypertension.

In Table 4, more than half of the participants [52.4%] had a family history of hypertension, and lifestyle factors such as smoking [30.6%] and alcohol intake [35.3%] were moderately common. The majority [58.1%] belonged to the middle socioeconomic class. This reflects the general demographic of hypertensive patients attending tertiary care hospitals in India.

Table 5 demonstrated that all three β-blockers caused a gradual and significant reduction in systolic and diastolic blood pressure over 60 days. Although the improvement was minimal at day 15, the reduction became significant

[p < 0.05] from day 30 onwards. Nebivolol showed the greatest fall in both systolic and diastolic blood pressure at each follow-up. By day 60, systolic BP reduced to 132.6 ± 7.4 mmHg in the Nebivolol group compared to 134.2 ± 7.8 mmHg and 136.0 ± 8.0 mmHg in Bisoprolol and Carvedilol groups, respectively. This finding suggests the superior antihypertensive efficacy of Nebivolol, which may be due to its nitric oxide–mediated vasodilatory properties. These results agree with Khan et al. [2021], who reported that Nebivolol provided better endothelial relaxation and blood pressure control than other β-blockers in hypertensive patients.

Table 6 shows significant improvement in lipid profiles over 60 days, especially in the Nebivolol group. Total cholesterol, triglycerides, and LDL cholesterol levels showed marked reduction [p < 0.05], whereas HDL cholesterol increased significantly after 30 days and continued to rise up to day 60. The lipid-modifying effects of Nebivolol are attributed to its antioxidant and nitric oxide–enhancing mechanisms. These results are consistent with Rai et al. [2020], who observed significant improvement in lipid metabolism with Nebivolol therapy compared to Bisoprolol and Carvedilol.

In Table 7, oxidative stress parameters improved significantly only after 60 days of treatment. At day 60, MDA levels reduced markedly [3.12 ± 0.54 nmol/mL in the Nebivolol group] while antioxidant enzyme levels [SOD and GPx] increased significantly [p < 0.001]. The early follow-up readings [15–45 days] showed no significant change, suggesting that prolonged therapy is required for oxidative stress correction. This antioxidant effect of Nebivolol has been confirmed by Mishra et al. [2019], who demonstrated that Nebivolol enhances antioxidant enzyme activity and reduces lipid peroxidation more effectively than traditional β-blockers.

As shown in Table 8, liver function tests [ALT, AST, ALP, total bilirubin, protein, and albumin] remained stable throughout the study with no statistically significant changes [p > 0.05], confirming the hepatic safety of all three β-blockers. Similar findings were reported by Prakash et al. [2018], who observed no hepatotoxic effects with long-term β-blocker use.

Similarly, Table 9 shows that renal function parameters such as serum creatinine, blood urea nitrogen, and uric acid remained within normal limits across all visits, with no significant differences [p > 0.05]. This suggests that none of the studied drugs adversely affected renal function. Previous studies have also confirmed that Nebivolol and Carvedilol are safe in patients with mild renal impairment.

Overall, the findings of this study indicate that Nebivolol is superior to Bisoprolol and Carvedilol in improving endothelial function, oxidative stress, and lipid profile, while maintaining excellent safety for hepatic and renal systems. The nitric oxide–mediated vasodilatory mechanism of Nebivolol contributes significantly to its enhanced cardiovascular protection.

CONCLUSIONS

This study compared Nebivolol, Bisoprolol, and Carvedilol in patients with hypertension over 60 days. All three drugs helped lower blood pressure, but Nebivolol showed the best results. The decrease in both systolic and diastolic blood pressure was greater in the Nebivolol group, with significant improvement seen after 30 days. Lipid levels also improved in all groups, but Nebivolol produced a larger drop in total cholesterol, triglycerides, and LDL, and a higher rise in HDL. Oxidative stress markers like MDA, SOD, and GPx improved more with Nebivolol after 60 days, showing better antioxidant and protective effects on blood vessels. Liver and kidney function remained normal in all patients, showing that all three drugs were safe. Overall, Nebivolol was the most effective and well-tolerated drug, providing better blood pressure control, lipid improvement, and antioxidant effects compared to Bisoprolol and Carvedilol.

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