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Clinical Effects of Classical and Vasodilator Beta Blockers in Treating Hypertension in Adults: A Systematic Review

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ABSTRACT

Background: Beta-blockers are preferred anti-hypertensive for patients with compelling indications. Vasodilator beta-blockers are of particular benefit in blood pressure control and other cardio-metabolic components with limited disturbance in metabolic parameters. There is inadequate evidence on the superiority of vasodilator beta-blockers over non-vasodilator beta-blockers in treating hypertension. Therefore, this systematic review aimed to generate evidence on the clinical effects of non-vasodilator and vasodilator beta-blockers in treating hypertension in adults

Methods: We searched articles in English published from January 2000 to January 2020 from the following databases: PubMed/Medline, Web of Science, and Google scholar. We considered the following search query: "clinical effectiveness AND vasodilator beta-blockers AND non-vasodilator beta-blockers AND adult hypertension treatment AND clinical trials".

Results: Nine randomized and controlled trials conducted in 3088 adult hypertensive patients were reviewed. All studies agreed on the comparable antihypertensive efficacy of vasodilating and non-vasodilating beta-blockers. Non-vasodilating beta-blockers significantly reduced heart rate, increased blood glucose, blood cholesterol, and triglycerides. Vasodilator beta-blockers were associated with better cardiometabolic risk reduction, better safety, and oxidative stress reduction.

Conclusion: The hypertensive efficacy of vasodilating and non-vasodilating beta-blockers were comparable. Vasodilating beta-blockers were associated with better cardiometabolic risk reduction, better safety profile, and better oxidative stress reduction. However, there is insufficient evidence regarding the superiority of vasodilating and non-vasodilator beta-blockers. Therefore, it is essential to conduct comprehensive clinical trials by involving different ethnic groups to determine the benefit of vasodilator beta-blockers over non-vasodilators for treating hypertension.

Keywords: Clinical effectiveness; Non-Vasodilator beta-blockers; Vasodilator beta-blockers; Hypertension; Systematic review

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1. Introduction

Beta-blockers are currently used for treating Ischemic Heart Diseases (IHDs), hypertension, cardiac arrhythmias, and Heart Failure (HF) [1]. Evidence suggests that initiating the treatment of hypertension with beta-blockers leads to modest Cardiovascular Disease (CVD) risk reductions and slight or no effects on mortality. Their antihypertensive effects are inferior to those of other antihypertensive medications, such as calcium channel blockers, diuretics, Angiotensin-Converting Enzyme Inhibitors (ACEIs), or Angiotensin Receptor Blockers (ARBs) [2, 3]. However, β-blockers are preferred hypertensive in patients with a compelling indication (IHD or HF) [4-7].

Beta-blockers vary concerning β-adrenoceptor selectivity, lipophilicity, inverse agonist and intrinsic sympathomimetic activity, membrane-stabilizing property, α-receptors blocking activity, nitric oxide-mediated vasodilating, and antioxidant properties [1, 8, 9]. Non-vasodilating beta-blockers negatively affect Systolic Blood Pressure (SBP) amplification through a reduction in heart rate and a contemporary increase in peripheral vasoconstriction, leading to an elevated reflection of the pressure wave from distal sites. Vasodilator β-Blockers may theoretically present more favorable effects on central hemodynamics. This is because of the downward shifting of arterial reflection sites, leading to declined amplitude and prolonged timing of wave reflection; thus, it may provide a lower impact on SBP amplification alternations [10].

Vasodilator beta-blockers are of particular benefit in blood pressure control and other cardio-metabolic components with limited disturbance in metabolic parameters [11]. Vasodilator beta-blockers may produce improved cardiovascular outcomes, compared with conventional, non-vasodilating beta-blockers. They are less likely to exhibit such classic beta-blockers side effects, as fatigue, reduced exercise capacity, Raynaud's phenomenon, cold extremities, bronchospasm, and erectile dysfunction. In addition to this, they lack the detrimental effects on insulin, glucose, and lipids associated with older beta-blockers [12].

Additional benefits of vasodilator beta-blockers are secondary to nitric oxide-mediated vasodilation. Nitric oxide dilates all blood vessels, exerts anti-inflammatory impacts in the blood vessel wall, inhibits platelet activation, smooths muscle cell proliferation, and vessel wall remodeling; therefore, it contributes to controlling vascular compliance. Nitric Oxide (NO) also participates in neurodegeneration and memory function, pulmonary vascular remodeling and apoptosis, atherosclerosis, and exercise-induced cardio-protection. The impairment of NO bioavailability leads to endothelial dysfunction; it is an essential event in the pathogenesis of numerous CVDs, such as hypertension, heart failure, and coronary artery disease [13]. Vasodilator beta-blockers can restore NO bioavailability [14, 15].

Despite the presence of NO-mediated vasodilation by vasodilator beta-blockers, no systematic review or meta-analysis is available comparing the treatment outcomes of vasodilating beta-blockers and non-vasodilating beta-blockers in hypertensive patients [16]. There is inadequate evidence on the superiority of vasodilator beta-blockers over non-vasodilator beta-blockers in treating hypertension [7]. Therefore, this systematic review aimed to generate comparative evidence on the clinical outcomes of classical beta-blockers and vasodilator-based treatment in adult hypertensive patients.

2. Methods

Data sources and search strategy

We searched articles written in English published from January 2000 to January 2020 from the following databases: PubMed/Medline, Web of Science, and Google Scholar with a systematic search query (see the supplementary file) (Appendix 1).

PICO for the systematic review

- Population: Adult patients aged ≥18 years with hypertension

- Intervention: Vasodilator beta-blockers (carvedilol, labetalol, carteolol, nebivolol, and celiprolol)

- Comparison: Non-vasodilator beta-blockers (propranolol, pindolol, timolol, penbutolol, nadolol, atenolol, acebutolol, betaxolol, bisoprolol, esmolol, and metoprolol).

- Outcome: Clinical outcomes (blood pressure, blood glucose, & cholesterol control, oxidative stress reduction & anti-inflammatory effects) of vasodilator beta-blockers

Study types

Randomized and controlled clinical trials comparing clinical outcomes (blood pressure, blood glucose, &

cholesterol control, oxidative stress reduction & anti-inflammatory effects) of vasodilator beta-blockers.

Inclusion and exclusion criteria

• Randomized and controlled clinical trials comparing clinical outcomes (blood pressure, blood glucose, & cholesterol control, oxidative stress reduction & anti-inflammatory effect) of vasodilator beta-blockers and classical or non-vasodilating beta-blockers therapy among adult hypertensive patients were included in the study.

• Randomized and controlled clinical trials comparing clinical outcomes (blood pressure, blood glucose, & cholesterol control, oxidative stress reduction & anti-inflammatory effect) of vasodilator beta-blockers and classical or non-vasodilating beta-blockers therapy among children with hypertension were excluded from the research.

• Studies conducted before January 2000 were also excluded.

• Articles disregarding clinical outcomes were excluded.

• Guidelines, review articles, short communications, and conference proceedings were excluded from the study.

• Articles not meeting the quality evaluation criteria were excluded from this study.

Study selection

From a total of 449 articles identified by literature search, 24 potentially relevant studies were selected. Next, after applying the inclusion and exclusion criteria listed above, only 16 articles were found to be relevant. To present strong evidence, we applied a quality check for the selected 16 articles; subsequently, 9 studies met our quality check and were considered for review [17] (Figure 1). Two investigators independently reviewed each study's abstract concerning the prespecified inclusion and exclusion criteria. In case of disagreement on the quality of the article, two authors discussed in the presence of the third author (BF). We included good-quality RCTs and pharmacoeconomic studies that assessed the clinical and cost-effectiveness of interventional therapies for treating true drug-resistant hypertension.

Data extraction and quality assessment

Two investigators abstracted study design information, baseline population characteristics, intervention details, and clinical outcomes from all included studies into standardized evidence tables. A second investigator evaluated these data for accuracy. Two investigators independently classified each study's quality as "good", or "poor" by predefined quality criteria based on the appraisal quality of RCTs (CONSORT & Delphi) tools [18-20] (Table 1). All research team members have evaluated the quality of included RCTs. Accordingly, poor-quality RCTs were excluded from the study. In general, good-quality studies did not meet at most one pre-specified criteria. A poor-quality study failed to meet at least two criteria and had a fatal limitation. Disagreements among the authors were managed through discussion in the presence of other authors.

Risk of bias assessment

Studies fulfilling our eligibility criteria were independently assessed for internal validity at the study level by two reviewers using the Cochrane Risk of Bias Tool for Randomized Controlled Trials. It contains 6 major biases that can occur in RCTs, including selection bias, reporting bias, performance bias, detection bias, attrition bias, and so on. Thresholds for good quality are meeting all criteria (i.e., low per domain); fair quality if one criterion is not met, and poor quality if one criterion is not met (i.e., high risk of bias for one domain) or two unclear criteria. Besides, there was an assessment, i.e., likely to have biased the outcome, and critical limitations that could invalidate the results or two or more criteria listed as high or unclear risk of bias [21] (Table 2). At each step, disagreements between two reviewers' assessments were resolved through discussion, e.g. by e-mail discussions or at plenary meetings for the whole group of reviewers.

Summary measures

We expressed the comparative clinical outcomes as Mean Difference (MD), the Relative Risk (RR), P-value of an outcome, and 95% Confidence Intervals (CIs); we considered a result significant if $P<0.05$.

Data synthesis and analysis

We qualitatively described and summarized the obtained evidence. We described the results of clinical outcomes of vasodilator beta-blockers for treating hypertension. We stratified the results by blood pressure reduction; reduction in blood glucose; cholesterol and triglyceride reduction; oxidative stress reduction, as well as the safety profile and adverse effects of vasodilator beta-blockers. Finally, major findings were discussed in comparison with other relevant studies.

Table 1. A quality appraisal of included RCTs based on Delphi and CONSORT instruments that pertain to the internal validity of RCTs

Dimensions of Quality	Randomization		Masking		Allocation Concealment		Handling of Withdrawals & Dropouts		Measures of Variability		Pre-Specified Analyses		Stopping Rules		Statistical Methods		Baseline Data		Address Multiplicity		Total Score %
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	
Badar et al. (2011) [22]	√		√			√	√		√		√		√		√		√		√		90
Bakris et al. (2004) [23]	√		√		√		√		√		√		√		√		√		√		100
Celik et al. (2006) [24]	√		√		√		√		√		√		√		√		√		√		100
Czuriga et al. (2003) [26]	√		√		√		√		√		√		√		√		√		√		100
Dhakam et al. (2008) [27]	√		√		√		√		√		√		√		√		√		√		100
Grassi et al. (2003) [28]	√		√		√		√		√		√		√		√		√		√		100
Hussain et al. (2017) [29]	√		√		√		√		√		√		√		√		√		√		100
Kumar et al. (2019) [30]	√		√		√		√		√		√		√		√		√		√		90
Tuncer et al. (2008) [25]	√		√		√		√		√		√		√		√		√		√		90

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3. Results

We abstracted 69 studies, reviewed 24 full-texts, and included 9 articles in the final review. In total, 3088 adult hypertensive patients were included in the RCTs. The studies were from 6 different countries: India [22], the USA [23], Turkey [24, 25], Hungary [26], UK [27], France [28], and Pakistan [29, 30] (Table 3).

Atenolol and nebivolol were the most extensive studies of non-vasodilator and vasodilator beta-blockers, respectively. Four studies compared nebivolol and atenolol [25, 27, 28]; two studies compared nebivolol and bisoprolol [26, 30]; two studies compared nebivolol and metoprolol [24, 30], and one study compared carvedilol and metoprolol [23].

A randomized and controlled trial in India compared the impacts of nebivolol and atenolol on metabolic parameters among adults with essential hypertension; they revealed no difference between these drugs on blood pressure reduction [22]. However, patients receiving atenolol presented a significant reduction in heart rate with a Mean±SD change of -13.33±0.84 versus -8±0.7311 BPM, respectively. Patients in atenolol arm also indicated a significant rise in FBG (mg/dL) (17.43±1.316 vs. 1.03±1.234) and total cholesterol (mg/dL) (21.83±1.034 vs. 0.53±0.658), triglyceride level (16.76±1.986 vs. 0.10±0.887), and LDL cholesterol (22.57±1.06 vs. 0.43±0.695), respectively. The mean change was statistically significant at P<0.001 [22].

Randomized and control trials were conducted among hypertensive adults with type 2 diabetes to compare the effects of carvedilol and metoprolol on glycemic and metabolic control in the USA. Accordingly, they reported no significant difference in Systolic Blood Pressure (SBP) (P=0.21) and Diastolic Blood Pressure (DBP) (P=0.53)

Table 2. Risk of bias of included RCTs based on cochrane risk of bias tool for randomized controlled trials

S.No	Reference	Sample Size	Selection Bias	Performance Bias (Blinding)	Detection Bias	Attrition Bias	Other Biases	Total
1	Badar et al. (2011) [22]	69	Low	Low	Low	Low	Low	Low
2	Bakris et al. (2004) [23]	1235	Low	Low	Low	Low	Low	Low
3	Celik et al. (2006) [24]	80	Low	Low	Low	Low	Low	Low
4	Czuriga et al. (2003) [26]	273	Low	Low	Low	Low	Low	Low
5	Dhakam et al. (2008) [27]	16	Low	Low	Low	Low	Low	Low
6	Grassi et al. (2003) [28]	205	Low	Low	Low	Low	Low	Low
7	Hussain et al. (2017) [29]	120	Low	Low	Low	Low	Low	Low
8	Kumar et al. (2019) [30]	1058	Low	Low	Low	Low	Low	Low
9	Tuncer et al. (2008) [25]	32	Low	Low	Low	Low	Low	Low

control at a 5-month follow-up. Similarly, changes in Fasting Blood Glucose (FBG) (P=0.10) and serum insulin level (P=0.51) were not significant [23]. Compared to carvedilol, metoprolol significantly reduced heart rate in (P<0.001), increased triglyceride level (P<0.001), body weight (P<0.001), urinary Albumin Creatinine Ratio (ACR) (P=0.003), Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) (P=0.004) and total cholesterol (P=0.001) [23].

A randomized and controlled trial conducted in Turkey compared nebivolol and metoprolol among adult hypertensive patients concerning their effect on oxidative stress and insulin resistance. These reports documented no difference between the two drugs on blood pressure control. However, heart rate was significantly reduced in the metoprolol arm (69.37±8.89), compared with nebivolol (57.88±8.10) (P<0.001). Malonyldialdehyde (mmol/L), insulin (µU/mL) resistance index, and HOMA-IR were significantly increased in the metoprolol arm compared with the nebivolol group [24].

Another RCT compared the short-term effects of nebivolol and atenolol on Doppler diastolic filling parameters in hypertensive patients; the authors concluded no difference in blood pressure control and heart rate at a 12-week follow-up. Nevibolol significantly improved early transmitral diastolic flow (E)/atrial contraction signal (A) ratio (P=0.05), Deceleration Time (DT) (P=0.05), and Isovolumetric Relaxation Time (IVRT) (P=0.003), compared with atenolol [25].

Another RCT conducted in Hungary compared the antihypertensive efficacy of nebivolol and bisoprolol among adults. This research revealed no significant difference between the study groups concerning blood pressure control, heart rate, and improvements in such symptoms as fatigue, dyspnea, and dizziness [26].

A randomized controlled trial conducted in the UK compared the effects of atenolol and nebivolol on central blood pressure and augmentation index; this investigation indicated no difference in central pressure reduction between the research groups. However, atenolol significantly decreased heart rate, compared to nebivolol (-23±2 Vs. -19±2) (P<0.001) and increased augmentation index (10±1 Vs. 6±1) (P=0.04) [27].

A study conducted in France compared the impacts of nebivolol and atenolol; the relevant data signified no difference in blood pressure control between these medications. However, the incidence of adverse effects was reported in the atenolol arm (41% vs. 20%) (P<0.001) [28].

A study conducted in Pakistan compared the effects of nebivolol and metoprolol on Neutrophil Lymphocyte Ratio (NLR) in mild to moderate hypertensive patients. Accordingly, no difference was observed between the

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Table 3. Selected RCTs comparing fixed-dose combination and loose combination therapies for the treatment of hypertension

S. No	1														
Study Reference	Badar et al. (2011) [22]														
Country	India														
Study Type	RCT														
Objectives	To compare the effects of nebivolol and atenolol on metabolic parameters in patients with essential hypertension.														
Cases	5 mg Nebivolol														
Controls	Atenolol														
Population	34-64 years hypertension														
Sample Size	69														
Measured Outcome/s	SBP after 24 weeks	DBP after 24 weeks	HR after 24 weeks	Fasting blood glucose	TC after 24 weeks	TG after 24 weeks	LDL after 24 weeks	HDL after 24 weeks	SBP after 24 weeks	DBP after 24 weeks	HR after 24 weeks	Fasting blood glucose	TC after 24 weeks	TG after 24 weeks	LDL after 24 weeks	HDL after 24 weeks
Mean Total (%)	Case	116.73±0.91	79.66±0.53	65.33±0.79	88.2±1.60	160.40±3.03	114.87±3.67	93.97±3.46	43.47±1.08	118.93±0.87	81.13±0.78	60.8±0.61	104.73±1.85	184.20±2.79	137.3±3.47	116.47±2.92	40.30±0.39
	Control	118.93±0.87	81.13±0.78	60.8±0.61	104.73±1.85	184.20±2.79	137.3±3.47	116.47±2.92	40.30±0.39	116.73±0.91	79.66±0.53	65.33±0.79	88.2±1.60	160.40±3.03	114.87±3.67	93.97±3.46	43.47±1.08
Change in Mean Difference from of Baseline Mean±SD	Case	43.2±1.505	18.6±1.332	-8±0.7311	1.03±1.234	0.53±0.658	0.10±0.887	0.43±0.695	0.1±0.402	43.2±1.505	18.6±1.332	-8±0.7311	1.03±1.234	0.53±0.658	0.10±0.887	0.43±0.695	0.1±0.402
	Control	41.2±1.7531	16±1.2930	-13.33±0.84	17.43±1.316	21.83±1.034	16.76±1.986	22.57±1.06	-3.97±0.301	41.2±1.7531	16±1.2930	-13.33±0.84	17.43±1.316	21.83±1.034	16.76±1.986	22.57±1.06	-3.97±0.301
95% CI for % Change in Treatment Difference																	
P for Treatment Difference	>0.05	>0.05	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001									

P for Treatment Difference			=0.21	=0.53	=0.10	=0.51	<0.001	=0.003	=0.004	=0.001	=0.40	<0.001	<0.001
95% CI for % Change in Treatment Difference			−2.60-0.58	−0.61-1.20	−8.73-0.78	−16.7-8.24	0.70-2.58	−25.31 to −5.87	−13.8 to −0.2	−4.60 to −1.15	−4.31-1.78	−13.68-−5.75	−1.43-−0.60
Change in Mean Dfference from of Baseline	**Mean±SD**	**Control**	−16.9(0.6)	−10.3(0.3)	10.6	−15.1	−8.3(0.4)	2.5	-2.0	−0.4	−2.7	13.2	1.2
		Case	−17.9(0.7)	76.8(0.3)	6.6	−19.4	−6.7(0.4)	-14.0	-9.1	-3.3	−4.0	2.2	0.17
Mean Total (%)		**Control**	132.3(0.6)	−10.0(0.4)	158.6	20.2	66.0(0.4)	13.3	6.2	185.6	96.7	186.0	98.2
		Case	131.3(0.7)	77.1(0.4)	154.7	19.6	67.6(0.4)	11.1	5.8	181.7	96.7	168.3	97.2
Measured Outcome/s			SBP after 5 months	DBP after 5 months	FBG in mg/ dL	Insulin, µIU/ mL	Heart rate in bpm	ACR, mg/g	HOMA-IR	Total choles-terol, mg/d	LDL levels, mg/d	Triglycerides, mg/dL	Body weight, kg
Sample Size			1235										
Population			36-85 hypertensive patients with type 2 DM										
Controls			50-200mg metoprolol tartrate bid										
Cases			6.25-25mg carvedilol bid										
Objectives			To compare the effects of carvedilol and metoprolol on glycemic and metabolic control in participants with DM and hypertension receiving RAS blockade, in the context of CV risk factors.										
Study Type			RCT										
Country			USA										
Study Reference			Bakris et al. (2004) [23]										
S. No			2										

P for Treatment Difference			=0.56	=0.15	<0.001	=0.03	=0.001	=0.003	>0.05	=0.7434	=0.8230	>0.05	>0.05
95% CI for % Change in Treatment Difference									86.0-96.2				
Change in Mean Dfference from of Baseline	**Mean±SD**	**Control**	- 26.17	-13.0	-19.6								
		Case	-22.7	-12.9	-6.6								
Mean Total (%)		**Control**	128.85±11.76	81.85±5.82	57.88±8.10	0.64±0.34	11.84±1.62	2.83±0.42	89.6%	−20.0±12.0	−16.0±6.8	68.1±7.5	−0.5±1.3
		Case	130.67±14.58	79.18±9.39	69.37±8.89	0.47±0.30	9.72±5.13	2.29±1.24	92%	−20.5±12.9	−15.7±6.4	68.7±8.5	−0.7±1.7
Measured Outcome/s			SBP after 6 months	DBP after 6 months	Heart rate in BPM	Malonyldialde-hyde (mmol/l)	Insulin (µU/ml), resistance index	HOMA-IR	% achieved DBP control target	SBP	DBP	Heart rate	Improvement in symptoms
Sample Size			80						273				
Population			Adult hypertensive patients						30-65 year Adults with mild to moderate essential hypertension				
Controls			100 mg daily metoprolol						5 mg bisoprolol				
Cases			5mg daily nebivolol						5 mg nebivolol or				
Objectives			To determine the effects of nebivolol on oxidative stress, insulin resistance, adiponectin, and plasma soluble P-selectin levels in hypertensive patients in comparison with metoprolol.						To evaluate the antihypertensive efficacy of nebivolol in comparison with bisoprolol in treating mild to moderate hypertension.				
Study Type			RCT						RCT				
Country			Turkey						Hungary				
Study Reference			Celik et al. (2006) [24]						Czuriga et al. (2003) [26]				
S. No			3						4				

P for Treatment Difference			=0.4	=0.5	=0.8	<0.01	=0.04	=0.2	<0.06	>0.05	>0.05	<0.001
95% CI for % Change in Treatment Difference												
Change in Mean Dfference from of Baseline	**Mean±SD**	**Control**				-23±2	10±1	-1.2±0.2	75±80	-18.2	–14.6	
		Case				-19±2	6±1	-1.0±0.3	100±33	- 19.1	- 14.8	
Mean Total (%)		**Control**	137±3	73±2	94±3	57±1	32±2	8.8±0.3	157(123)	137±14.1	85.9±7.7	41%
		Case	136±3	75±2	95±2	61±2	28±2	9.1±0.3	138(201)	138.2±12.0	85.6±6.9	20%
Measured Outcome/s			Brachial SBP	Brachial DBP	MAP in mmHg	Heart rate beat/min	% AIx	[a]PWV m/s	N-terminal proBNP pg/ml	SBP after 12 weeks	DBP after 12 weeks	Incidence of side effects
Sample Size						16					205	
Population						Never treated Adult hypertensive patients					Adults	
Controls						Atenolol 50 mg and placebo					Atenolol 100mg	
Cases						Nebivolol 5 mg and placebo					Nebivolol 5mg	
Objectives						To compare the effects of atenolol and nebivolol on central blood pressure and augmentation index.					To compare the efficacy and tolerability of nebivolol, and atenolol.	
Study Type						RCT					RCT	
Country						UK					France	
Study Reference						Dhakam et al. (2008) [27]					Grassi et al. (2003) [28]	
S. No						5					6	

P for Treatment Difference			=0.68	=0.17	=0.001	=0.009	=0.02	=0.004	=0.16	=0.28	=0.39	=0.23
95% CI for % Change in Treatment Difference									0.53-1.11	0.47-1.24	0.65-1.18	0.56-1.15
Change in Mean Dfference from of Baseline	**Mean±SD**	**Control**	- 22.5	- 11.2								
		Case	-20.5	-10.5					HR=0.77	HR= 0.76	HR= 0.88	HR=0.80
Mean Total (%)		**Control**	136±8	83±10	9.3±4.72	7.4±4.5	2.1±1.45	4.4±2.7	57(11.49%)	35(7.0%)	81(16.3%)	60(12.09%)
		Case	131±11	80±11	7.6±3.1	4.9±3.2	2.4±0.8	2.2±1.5	49(9.8%)	27(5.4%)	72(14.4%)	49(9.8%)
Measured Outcome/s			SBP reduction	DBP reduction	WBC count × 109/L	Neutrophil count × 109/L	Lymphocyte count × 109/L	Reduction in NLR ratio	All case mortality after one year	CV mortality	All case Hospitalization	CV Hospitalization
Sample Size			120						1058			
Population			Adults						Adults, 35-75			
Controls			metoprolol 50–100 mg daily						Standard therapy + bisoprolol			
Cases			nebivolol 5–10 mg daily						Standard therapy + Nebivolol			
Objectives			To investigate the effect of nebivolol on NLR in mild to moderate hypertensive patients, in comparison with metoprolol.						To Compare nebivolol and bisoprolol for CV mortality in hypertensive patients.			
Study Type			RCT						RCT			
Country			Pakistan						Pakistan			
Study Reference			Hussain et al. (2017) [29]						Kumar et al. (2019) [30]			
S. No			7						8			

S. No	Study Reference	Country	Study Type	Objectives	Cases	Controls	Population	Sample Size	Measured Outcome/s	Mean Total (%)		Change in Mean Difference from of Baseline		95% CI for % Change in Treatment Difference		P for Treatment Difference
										Mean±SD						
										Case	Control	Case	Control			
9	Tuncer et al. (2008) [25]	Turkey	RCT	To compare the short-term effects of nebivolol and atenolol on Doppler diastolic filling parameters in hypertensive patients.	Nebivolol 5mg/day	Atenolol 50 mg/day	Adults	32	SBP after 12 weeks	131.4±9.6	141.1±14.5					=0.18
									DBP after 12 weeks	81.4±8.6	85.6±8.8					=0.44
									Heart rate	66.7±9.8	70.7±9.7					=0.34
									E, m/sec	0.87±0.15	0.62±0.19					=0.08
									A, m/sec	0.72±0.12	0.68±0.26					=0.77
									E/A ratio	1.23±0.18	1.01±0.22					=0.05
									DT, msec	173.6±24.7	202.2±33.1					=0.05
									IVRT, msec	85.7±10.2	100.0±11.2					=0.003

NB: AIx, Aortic augmentation index; aPWV, aortic Pulse Wave Velocity; BP, Blood Pressure; MAP, Mean Arterial Pressure; proBNP, Pro Brain type Natriuretic Peptide; PP, Pulse Pressure; apoB/apoAI, apolipoprotein AI; apoB, apolipoprotein B ratio; ICAM-1, Intercellular Adhesion Molecule-1; ACR, urinary Albumin/Creatinine Ratio; CI, Confidence Interval; HDL, High-Density Lipoprotein; HOMA-IR, Homeostatic Model Assessment-Insulin Resistance; LDL, Low-Density Lipoprotein; NLR, Neutrophil-Lymphocyte Ratio; A, atrial contraction signal; DT, Deceleration Time; E, Early transmitral diastolic flow; IVRT, Isovolumetric Relaxation Time; TC, Total Cholesterol; TG, Triglyceride; HR, Heart Rate

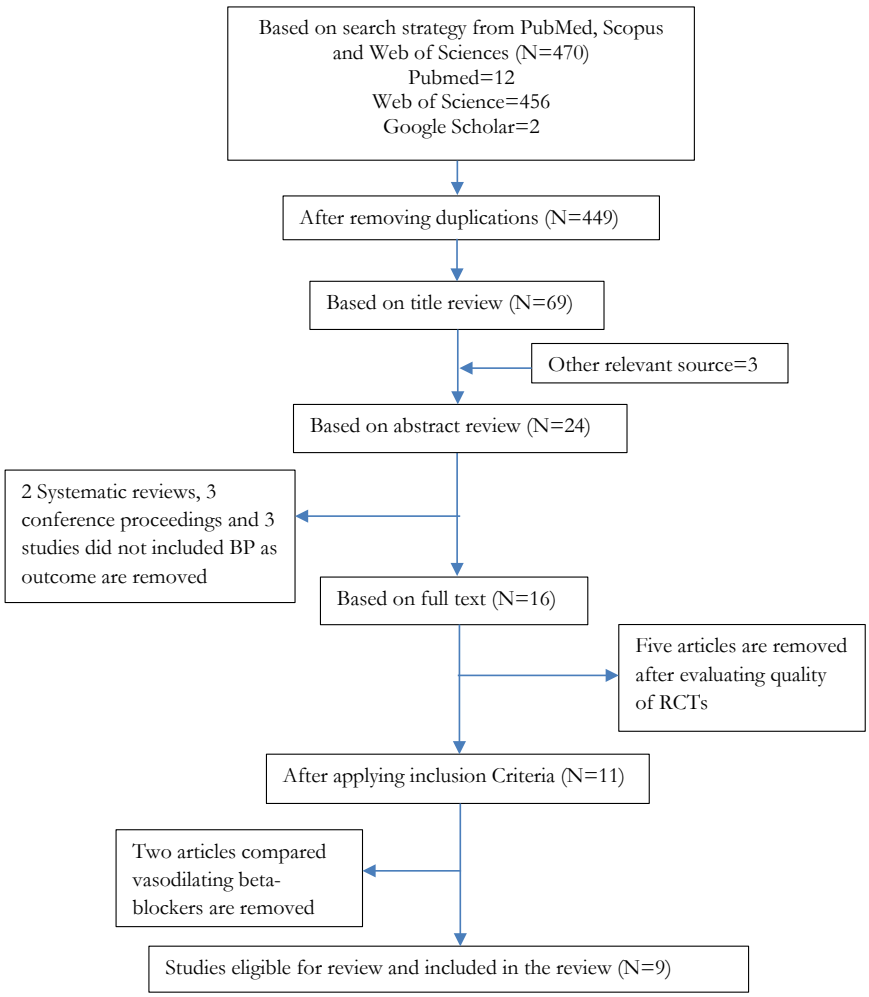

Figure 1. PRISMA Flowchart representing the result of search and the number of articles excluded and eligible for review

two drugs in blood pressure control. However, nebivolol presented a better effect on NLR reduction (2.2±1.5 vs. 4.4±2.7) (P=0.004) [29]. Another RCT in the same country compared nebivolol and bisoprolol respecting cardiovascular mortality in hypertensive patients. This research demonstrated no difference in overall mortality or CV disease mortality between the two drugs [30].

4. Discussion

In this systematic review, we compared the clinical outcomes of vasodilating blockers and non-vasodilating beta-blockers among adult hypertensive patients by 9 RCTs. A total of 3,088 adult hypertensive patients were included in the explored RCTs. The selected studies were from 6 countries; India [22], the USA [23], Turkey [24, 25], Hungary [26], UK [27], France [28], and Pakistan [29, 30].

The hypertensive efficacy of vasodilating and non-vasodilating beta-blockers was comparable. However, a significant reduction in the heart rate with non-vasodilating beta-blockers was reported. Similarly, non-vasodilating beta-blockers were associated with a significant increase in blood glucose, total cholesterol, LDL cholesterol, and triglycerides. However, vasodilator beta-blockers were associated with better Cardiometabolic Risk (CMR), including the Metabolic Syndromes (METs), better stress reduction, and declined sub-clinical inflammation markers [11, 22-30].

Concerning heart rate, non-vasodilator beta-blockers caused a significant reduction in heart rate, compared with vasodilator beta-blockers. A study conducted in India compared the role of nebivolol and atenolol; the related results suggested that patients in the atenolol arm presented a significant reduction in heart rate with a Mean±SD change of -13.33±0.84 vs. -8±0.7311 BMT, respectively (P<0.001) [22].

A study conducted in the USA revealed that compared to carvedilol, metoprolol significantly reduced heart rate, increased triglyceride level, body weight, ACR, HOMA-IR, and total cholesterol [23]. Similarly, an RCT conducted in Turkey indicated that heart rate was significantly reduced in the metoprolol arm, compared with the nebivolol group (P<0.001) [24]. An RCT conducted in the UK presented that atenolol significantly reduced heart rate, compared to nebivolol (P<0.001) [27].

However, an RCT conducted in Turkey revealed no difference in heart rate after 12 weeks of follow-up [25]. A similar study in Hungary compared the antihypertensive efficacy of nebivolol and bisoprolol among adults; subsequently, there was no significant difference between the research groups concerning heart rate [26].

Concerning FBG, a study conducted in India documented that patients who were taking atenolol provided a statistically significant rise in FBG (17.43±1.316 vs. 1.03±1.234 mg/dL, respectively) [22]. Similarly, different studies suggested more favorable glycemic control with vasodilating beta-blockers [31-33]. They are less likely to exhibit such classic beta-blockers adverse effects as fatigue, reduced exercise capacity, Raynaud's phenomenon, cold extremities, bronchospasm, and erectile dysfunction. In addition to this, they lack the detrimental effects on insulin, glucose, and lipids associated with older beta-blockers [12].

An RCT conducted among African Americans in the USA revealed a significant increase in body weight metoprolol (P<0.001), urinary Albumin/Creatinine Ratio (ACR) in mg/g (P=0.003), HOMA-IR (P=0.004), and total cholesterol (P=0.001) [23]. This finding was in line with those of the previous trials signifying that non-beta-blockers are associated with weight gain. This could be due to the beta-blockade-induced decrease in metabolic rate and their negative effects on energy metabolism [34]. However, the vasodilating beta-blockers present a neutral effect on body weight [35]. Managing obesity and overweight hypertensive patients with non-vasodilator beta-blockers may be more difficult. This effect may pose a challenge to non-pharmacologic therapies for hypertension and other cardiovascular diseases.

However, an RCT conducted among hypertensive adults with type 2 diabetes to compare carvedilol and metoprolol on glycemic and metabolic control in African Americans suggested no significant changes in FBG (P=0.10) and serum insulin level (P=0.51) [23]. This could be due to the blunt response of African Americans to nitric oxide-mediated vasodilation [13].

Concerning insulin resistance, the insulin resistance index (μU/mL) was significantly increased in the metoprolol arm, compared with the nebivolol group [24]. This result was consistent with those of studies documenting improved insulin sensitivity and reduced risk for the development of diabetes with carvedilol, compared to metoprolol [11, 35]. Another study indicated decreased insulin sensitivity with metoprolol, compared with nebivolol [36].

Concerning blood cholesterol level, a study in India demonstrated that atenolol significantly raised total cholesterol, triglyceride level, and LDL cholesterol. Atenolol also significantly reduced High-Density Lipoprotein (HDL) cholesterol levels [22]. This could be due to the effect of beta-blockade on the management of obesity and overweight [34]. Obesity is a risk factor for atherosclerotic vascular disease. Furthermore, a vascular endothelial fibrinolytic function is impaired in adults with prehypertension and hypertension; it also plays a mechanistic role in the development of atherothrombotic events. However, carvedilol provides a neutral or favorable effect on the levels of triglycerides and HDL cholesterol [37].

An RCT conducted in Turkey compared the short-term effects of nebivolol and atenolol on Doppler diastolic filling parameters in hypertensive patients; the related results indicated that nevibolol significantly improved early transmitral diastolic flow (E)/atrial contraction signal (A) ratio, DT, IVRT, compared to atenolol [25]. This result was similar to those of another RCT, signifying that nebivolol treatment significantly increased the reactivity of the brachial artery and flow-mediated endothelial-dependent vasodilation, compared with bisoprolol [38]. This could be attributed to the nitric oxide-mediated vasodilation of nebivolol [13]. Using nebivolol was associated with a substantial increase in the capacity of the endothelium to release tissue Plasminogen Activator (t-PA) following long-term treatment with nebivolol, compared to metoprolol [39].

Regarding safety, an RCT conducted in Hungary compared the antihypertensive efficacy of nebivolol and bisoprolol in adults. Consequently, they identified no significant difference between the study groups concerning improvement in symptoms, such as fatigue, dyspnea, and dizziness [26]. Another RCT in the same country compared nebivolol and bisoprolol for cardiovascular mortality in hypertensive patients; the collected data revealed no difference in overall mortality or CVD mortality between the two medicines [30].

However, a study conducted in France compared the efficacy and tolerability of nebivolol and atenolol and reflected a higher incidence of adverse effects in the atenolol arm (41% vs. 20%) (P<0.001) [28]. Similarly, retrospective research compared hospitalization risk due to CV events among different beta-blockers; it was observed that nebivolol monotherapy was associated with lower CV-related hospitalization risk, compared to atenolol and metoprolol [40]. Similarly, a retrospective cohort study compared the risk of hospitalization for cardiovascular events respecting β-Blockers in hypertensive patients. The obtained data indicated that atenolol and metoprolol cohorts presented greater risks of hospitalization for a composite event (MI, angina, HF, stroke), compared to nebivolol users (adjusted hazard ratios [(95% CI) atenolol: 1.68 (1.29, 2.17); metoprolol: 2.05 (1.59, 2.63); P<0.001] [41].

Concerning oxidative stress and inflammation vasodilator, beta-blockers reflected a better reduction in oxidative stress and neutrophil and lymphocyte ratio (a marker of subclinical inflammation), compared to non-vasodilating beta-blockers. A study conducted in Pakistan reported a significant reduction in NLR following nebivolol use [29]. An RCT conducted in Turkey signified that malonyldialdehyde level, i.e., a marker of oxidative stress was significantly increased in the metoprolol arm, compared with the nebivolol group [24]. Nebivolol is free radicals scavenger; thereby it reduces oxidative stress [42]. Additionally, it may present anti-inflammatory pleiotropic benefits, which may be protective for atherosclerotic disease [11].

Overall, vasodilator beta-blockers have better cardiometabolic risk reduction and safety profiles. Additionally, vasodilator beta-blockers cost comparable to or less than non-vasodilator beta-blockers. Pocket evidence suggests that switching hypertensive patients from non-vasodilating to vasodilating beta-blocker could significantly reduce CVD-related healthcare resource use [43-45]. However, the quality and size of RCTs were small and specific to the explored countries. Multinational comparative trials involving different ethnic groups are critical. This view is supported by the recent hypertension treatment guideline of the European society of cardiology [7].

5. Conclusion

The antihypertensive efficacy of vasodilating and non-vasodilating beta-blockers was comparable. Non-vasodilator beta-blockers reduced heart rate increased plasma glucose, increased blood cholesterol, and triglycerides. Vasodilating beta-blockers were associated with better safety, better stress, and inflammatory marker reduction. There is insufficient comparative evidence regarding the superiority of vasodilating and non-vasodilator beta-blockers in a wider population. Therefore, it is essential to conduct comprehensive clinical trials to determine the benefits of vasodilator beta-blockers over non-vasodilator beta-blockers on the clinical outcomes of hypertensive patients.

Ethical Considerations

Compliance with ethical guidelines

This condition did not apply to the present research. This was a systematic review study and we have only used published articles.

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Authors contributions

Conceptualization and supervision, methodology: All authors; Writing – original draft: Mende Mensa Sorato and Behzad Fatemi, Writing – review & editing: Majid Davari.

Conflict of interest

The authors declared no conflicts of interest.

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Appendix 1. Supplementary file (Search strategy)

PubMed: ((((((((("treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"[All Fields] OR ("treatment"[All Fields] AND "outcomes"[All Fields]) OR "treatment outcomes"[All Fields]) AND (("vasodilator agents"[Pharmacological Action] OR "vasodilator agents"[MeSH Terms] OR ("vasodilator"[All Fields] AND "agents"[All Fields]) OR "vasodilator agents"[All Fields] OR "vasodilator"[All Fields]) AND ("adrenergic beta-antagonists"[Pharmacological Action] OR "adrenergic beta-antagonists"[MeSH Terms] OR ("adrenergic"[All Fields] AND "beta-antagonists"[All Fields]) OR "adrenergic beta-antagonists"[All Fields] OR ("beta"[All Fields] AND "blockers"[All Fields]) OR "beta blockers"[All Fields]))) OR ("carvedilol"[MeSH Terms] OR "carvedilol"[All Fields])) OR ("carteolol"[MeSH Terms] OR "carteolol"[All Fields])) OR ("nebivolol"[MeSH Terms] OR "nebivolol"[All Fields])) OR ("celiprolol"[MeSH Terms] OR "celiprolol"[All Fields])) AND (non-vasodilator[All Fields] AND ("adrenergic beta antagonists"[Pharmacological Action] OR "adrenergic beta-antagonists"[MeSH Terms] OR ("adrenergic"[All Fields] AND "beta-antagonists"[All Fields]) OR "adrenergic beta-antagonists"[All Fields] OR ("beta"[All Fields] AND "blockers"[All Fields]) OR "beta blockers"[All Fields]))) OR (classical[All Fields] AND ("adrenergic beta-antagonists"[Pharmacological Action] OR "adrenergic beta-antagonists"[MeSH Terms] OR ("adrenergic"[All Fields] AND "beta-antagonists"[All Fields]) OR "adrenergic beta-antagonists"[All Fields] OR ("beta"[All Fields] AND "blockers"[All Fields]) OR "beta blockers"[All Fields]))) AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields])) AND (("hypertension"[MeSH Terms] OR "hypertension"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]))) AND ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trials"[All Fields]) AND Clinical Trial[ptyp].

Web of Science: "Treatment outcomes AND vasodilator beta-blockers OR Carvedilol OR labetalol OR carteolol OR nebivolol OR celiprolol AND non-vasodilator beta-blockers OR classical beta-blockers AND Adult Hypertension Treatment AND Clinical Trials".

Google Scholar: "Treatment outcomes AND vasodilator beta-blockers OR Carvedilol OR labetalol OR carteolol OR nebivolol OR celiprolol AND non-vasodilator beta-blockers OR classical beta-blockers AND Adult Hypertension Treatment AND Clinical Trials".