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Efficacy of nebivolol/valsartan combined pill for anti-hypertensive therapy: A systematic review and meta-analysis

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Keywords: Nebivolol; Valsartan; Antihypertensive therapy; Hypertension; Systolic blood pressure; Diastolic blood pressure.

Abbreviations: ARB: Angiotensin Receptor Blockers; RAAS: Renin-Angiotensin Aldosterone System; SPC: Single-Pill Combination; N/V: Nebivolol/Valsartan; MeSH: Medical Subject Headings; RCTs: Randomized Controlled Trials; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ASH: American Society of Hypertension; PRA: Plasma Renin Activity; ACE: Angiotensin-Converting Enzyme; CCBs: Calcium Channel Blockers; (I2): I-squared; (Chi2): Chi-squared.

Abstract

The novel Nebivolol/Valsartan (N/V) combination pill shows superior efficacy in managing hypertension compared to nebivolol, valsartan monotherapies, or valsartan/amlodipine. A systematic review of Randomized Controlled Trials (RCTs) from three databases up to July 2024 included studies comparing the N/V combination pill to these therapies in hypertensive patients. A meta-analysis was performed to estimate the mean differences in central Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) using Review Manager 5.4. Results were presented as forest plots and 95% Confidence Intervals (CIs). Three RCTs, comprising a total of 4365 patients, met the inclusion criteria. The N/V combination pill significantly reduced SBP (MD: -2.67; 95% CI: -4.54 to -0.81) and DBP (MD: -1.31; 95% CI: -2.42 to -0.20) compared to nebivolol alone. When compared to valsartan-only or valsartan/amlodipine, N/V combination pill showed significant reductions in SBP (MD: -2.65; 95% CI: -4.38 to -0.92); however, the change in DBP was not statistically significant (MD: -2.26; 95% CI: -6.46 to 1.94). The N/V combination pill significantly lowers SBP and DBP than valsartan, valsartan/amlodipine, or nebivolol alone. Limitations include a small sample size, no gender-specific data, and unreported side effects. Further research is important to confirm its safety and efficacy across different populations.

Introduction

Hypertension affects approximately half of the population, contributing to over 680,000 deaths in the US in 2020, with uncontrolled hypertension leading to complications such as heart disease and stroke [1]. It is clinically characterized by blood pressure that exceeds the normal range of 120/90 mm HG. Recommended hypertension management is non-pharmaceutical therapy, such as lifestyle modifications; Angiotensin Receptor Blockers (ARB) and β-blockers are primary pharmaceutical interventions when non-pharmaceutical therapy is ineffective [2,3]. Valsartan's ARB mechanism of action disrupts the Renin-Angiotensin-Aldosterone System (RAAS). This prevents angiotensin II from causing vasoconstriction, making it an effective drug for managing hypertension. This allows it to control blood pressure and decrease mortality and morbidity rates [4,5]. Nebivolol is a third-generation selective β-blocker with vasodilatory properties [6]. It is a favorable antihypertensive drug as it has a beneficial cardiac effect and tolerability, particularly in its L-enantiomer form [7,8].

The combination of a vasodilating β-blocker (nebivolol) and an angiotensin II receptor blocker (valsartan) in adults with hypertension is likely to cause a more significant reduction in blood pressure compared to the monotherapy dosage [9]. Moreover, decreasing the pill burden can increase patient compliance, improving hypertension management and patient outcomes [10-12]. Despite these potential advantages, findings from some studies [13,14] suggest that the combination of β-blockers and RAAS inhibitors is not as effective as expected due to overlapping mechanisms of renin suppression. However, recent research shows that the Single-Pill Combination (SPC) of nebivolol and valsartan demonstrates antihypertensive efficacy over its monotherapy component [15].

Due to insufficient clinical trials, the efficacy and safety of the Nebivolol/Valsartan (N/V) combination pill are not adequately addressed, and substantial research gaps exist. Most present research [9,16] focuses on these medications individually or in combination with other drugs without directly assessing their synergistic potential. This is due to the shortage of large-scale, long-term studies and variations in the study methodologies, patient demographics, and treatment endpoints. So, there is a need to arrange the already present data methodologically.

This meta-analysis aims to address this gap by directly assessing the combination's potential for blood pressure lowering and its efficacy, safety, and tolerability. Thus, it provides an effective treatment option for hypertensive patients. Future clinical guidelines are anticipated to benefit from these findings, which will enhance the management of hypertension in a wide range of patient demographics.

Methods

This meta-analysis and systematic review complied with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for meta-analyses [17]. The International Prospective Register of Systematic Reviews (PROSPERO) has registered this review with the identification number CRD42024595625. Our meta-analysis did not require ethical approval.

Search strategy

A comprehensive search was conducted to evaluate the efficacy of nebivolol and valsartan as combination therapy. Searches were conducted in PubMed, Google Scholar, and Cochrane databases were searched from establishment till July 2024. The search strategy was based on a combination of the following Medical Subject Headings (MeSH) terms and keywords such as "nebivolol," "valsartan," "beta-blocker," "angiotensin II receptor blocker," "angiotensin receptor blockers," "high blood pressure," "randomized controlled trials," "antihypertensive agents," "ARB," "systolic blood pressure," "diastolic blood pressure," "placebos," and "hypertension." There were no limitations regarding language or publication date. Additional relevant studies were identified by scrutinizing the references of the retrieved articles.

Selection of studies

The papers included in this meta-analysis were selected based on strict inclusion criteria consisting of only Randomized Controlled Trials (RCTs) with hypertensive adults 18 years of age and above. The interventions assessed were nebivolol and/or valsartan and valsartan/amlodipine in combination therapy at any dose where Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) before and after treatment were compared. Studies were excluded if they had a non-randomized design, were not peer-reviewed, had a sample that included populations other than hypertensive adults, or did not report on the mentioned interventions or outcomes.

Data collection process and data items

Two researchers reviewed titles and abstracts independently and examined full texts to determine inclusion criteria. Discrepancies were resolved through discussion or by consulting a third reviewer. Three reviewers then extracted data into an Excel spreadsheet to ensure consistency. Extracted data items included trial name, year of publication, study design, sample size, doses and regimen of nebivolol and valsartan, comparator, follow-up duration, and primary outcome variables such as SBP and DBP. Central blood pressure, measured in the ascending aorta and major central arteries, is a more accurate marker of cardiovascular load than peripheral blood pressure. It is affected by arterial stiffness and amplification, allowing evaluation of cardiovascular risk and hypertension management.

Statistical analysis

Review Manager software version 5.4 was used to synthesize data from RCTs investigating the effects of N/V combined pills on hypertensive patients. The mean differences and standard error of change in central SBP and DBP variables were used to express the results. The effect size was calculated using the inverse variance algorithm. The effect size of continuous outcomes was estimated using mean differences and standard errors with 95% Confidence Intervals (CIs), and the findings were visualized using a forest plot. The I-squared (I^2) index and the chi-squared (Chi^2) test were used for each analysis to assess heterogeneity, with a P value of 0.1 indicating significant heterogeneity among the included studies. A meta-analysis of outcome measures was conducted using the random-effects model, and a p-value of less than 0.05 was considered statistically significant.

Quality assessment

The risk of bias involved assessing the quality of the selected studies using the Revised Cochrane Risk of Bias 2 tool for randomized trials [18]. The appraisal focused on critical domains such as adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and free of other biases. The studies were judged to have a low risk of bias when all domains were rated as low risk, but there were some concerns when one or more domains were rated as having unclear risks [18]. Finally, there was a high risk of bias if at least one domain was rated as high risk or if multiple domains were judged to have some concerns that lowered confidence in the results.

Results

Literature search results

A search through three electronic databases yielded 5296 study results. After the screening, three studies were identified that compared the results of change in SBP and DBP of N/V combined pill (2 vs nebivolol and 3 vs valsartan or valsartan/amlodipine). The PRISMA chart summarizing the literature search results is attached in Figure 1.

Study characteristics and quality assessment

A total of 4365 patients above the age of 18 with diagnosed hypertension were assigned to either the N/V combined pill (intervention), the nebivolol-only pill (control 1), the valsartan-only or valsartan/amlodipine pill (control 2). Follow-up ranged from 4 to 12 weeks. The baseline characteristics of all trials are summarized in the Table 1.

Two of the included studies are of high methodological quality, while one carries a significant risk of bias, as shown in the table below.

Combined pill vs. nebivolol

Central systolic blood pressure: Two studies reported the outcome of central SBP. The random model showed a statistically significant difference between those taking combined pills and those taking nebivolol alone (MD: -2.67; 95% CI: -4.54 to -0.81; p=0.005), as shown in Figure 2A. There was no heterogeneity among the included studies (I^2=0%).

Central diastolic blood pressure: Two studies reported the outcome of central DBP. There was statistically significant significance between those taking combined pills and those taking nebivolol alone (MD: -1.31; 95% CI: -2.42 to -0.20; p=0.02), as shown in Figure 2B. No heterogeneity was reported for this outcome (I^2=0%).

Combined pill vs (valsartan or valsartan/amlodipine)

Central systolic blood pressure: Three studies reported the outcome of central SBP. As illustrated in Figure 2C, a statistically significant difference was found between those taking combined pills and those taking valsartan alone or valsartan/amlodipine together (MD: -2.65; 95% CI: -4.38 to -0.92; p=0.003). There was no heterogeneity reported for this outcome (I^2 = 0%).

Central diastolic blood pressure: Three studies reported the outcome of central DBP. As depicted in Figure 2D, no statistically significant difference was found between those taking combined pills and those taking valsartan alone or valsartan/amlodipine together (MD: -2.26; 95% CI: -6.46 to 1.94; p=0.29). Moderate heterogeneity was reported for this outcome (I^2=57%).

Table 1: Study characteristics included in the meta-analysis.

Author (Year)	Study design	Sample size	Population	Intervention	Comparator	Duration	Primary outcomes	Results
Farag et al, (2018) [27]	RCT	62	160	Nebivolol (5 mg)/ Valsartan (160 mg)	Valsartan/ Amlodipine	12 weeks	SBP (mm Hg), DBP (mm Hg)	SBP = -15.59 mm Hg, DBP = -7.27 mm Hg
Izzo et al, (2015) [28]	RCT	26	44	Nebivolol (40 mg)/ Valsartan (320 mg)	Valsartan/ Amlodipine	4 weeks	SBP (mm Hg), DBP (mm Hg)	SBP = -23 mm Hg, DBP = -3 mm Hg
Giles et al, (2014) [25]	RCT	555	4161	Nebivolol (10 mg)/ Valsartan (160 mg)	Valsartan/ Amlodipine	6 weeks	SBP (mm Hg), DBP (mm Hg)	SBP = -17.7 mm Hg, DBP = -14.8 mm Hg

RCT: Randomized Controlled Trial; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Table 2: Details the risk of bias assessment of the included studies.

Author (year)	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Free of other bias
Farag et al, (2018) [27]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Moderate risk
Izzo et al, (2015) [28]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	High risk
Giles et al, (2014) [25]	low risk	Low risk	low risk	low risk	unclear risk	low risk	low risk

PRISMA diagram of study selection

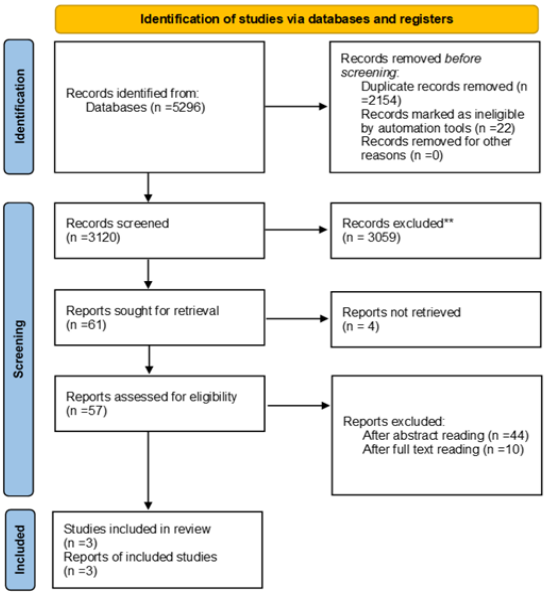


Figure 1: The PRISMA flow diagram outlines the steps for conducting a literature search and the rationale for excluding studies.

Forest plots of central blood pressure outcomes

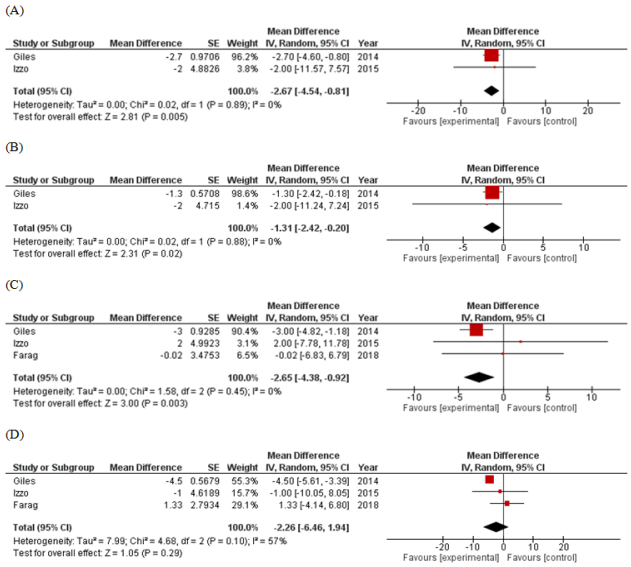


Figure 2: Forest plots depicting the changes in central blood pressure outcomes: **(A)** Forest plot showing the change in central Systolic Blood Pressure (SBP) for the combined pill versus nebivolol. **(B)** Forest plot showing the change in central Diastolic Blood Pressure (DBP) for the combined pill versus nebivolol. **(C)** Forest plot showing the change in central SBP for valsartan versus valsartan/amlodipine. **(D)** Forest plot showing the change in central DBP for valsartan versus valsartan/amlodipine.

Discussion

This meta-analysis of 4365 patients shows the efficacy of N/V combined pills and their role in reducing central blood pressure. To our knowledge, this is the first statistical analysis to demonstrate a significant decrease in central SBP on the consumption of N/V combined pills compared to nebivolol and valsartan alone or valsartan/amlodipine combination. This highlights the potential benefits of combination therapy in the management of hypertension.

The efficacy of the N/V combined pill was evident in not only the reduction of central SBP but also central DBP in contrast to the effect of the nebivolol single pill. This finding implies that combining a β-blocker with an ARB can improve blood pressure control, potentially attributed to both drugs' synergistic effect or the paired mechanisms of action. The studies included in our meta-analysis revealed a lack of heterogeneity (I^2=0%) for both SBP and DBP, which adds to the confidence and strength of the findings above from this study. These results align with research deduced from a review article published in 2021 that combination therapy can be used as an initial antihypertensive therapy and offers superior control of blood pressure compared to monotherapy approaches [19].

Comparing the effects of the N/V combination tablet with valsartan alone or the valsartan/amlodipine combination, the N/V pill significantly reduced SBP. However, it did not reveal a statistically significant effect on the DBP. The heterogeneity detected in the analysis of DBP (I^2=57%) in this study indicates variability in the study methodology or the population, which may have affected the study outcomes. Despite this, the reduction in SBP is significant. It is remarkable since it underscores the possibility of the N/V combined pill for SBP management, even in those cases where valsartan or amlodipine monotherapy might not be adequate. No subgroup analysis was done due to the lack of data provided in the included clinical trials.

According to a 2010 American Society of Hypertension (ASH) Position Statement, the combination of a β-blocker and an ARB is a less effective drug regimen for the management of hypertension because there was no significant reduction in blood pressure when the two drugs were consumed together. However, these combined pills were observed to have particular benefits on mortality, particularly among post-myocardial infarction as well as heart failure patients [20].

Besides the evidence-based blood pressure-lowering properties of nebivolol, there seem to be other factors that contribute when used in combination with valsartan. Monotherapy with nebivolol has been shown to alleviate Plasma Renin Activity (PRA), resulting in increased cardiovascular mortality, commonly noted with valsartan [21,22]. While Giles *et al.* noted lower circulating aldosterone levels in all treatment arms, the high-dose combination drug regimen resulted in more significant blood pressure reduction [23]. This potential synergy might have made N/V a more unique and effective combination, unlike the β-blocker/ARB combinations studied in the past [3].

The findings from this meta-analysis suggest several implications for clinical practice. The combination is most beneficial in patients who have indications for both nebivolol and valsartan. In a combined pill, the efficacy of both drugs is increased synergistically. Despite the consequential reduction in blood pressure, the combination drugs are effective in post-myocardial infarction patients with metabolic syndrome such as diabetes who indicate a β-blocker. Patients with chronic kidney disease may also benefit if an Angiotensin-Converting Enzyme (ACE) inhibitor cannot be given. This would make N/V a more favorable option, especially for those who wish to avoid metabolic effects with other beta-blockers [24,25].

Further, a combined pill will reduce the pill burden on patients. A single pill is more likely to improve compliance as this reduces the need to take more medications. Compliance falls with a two-drug regimen as opposed to a once-daily pill

that contains both drugs. Additionally, the single pill will also be cost-effective. Cost comparisons should be evaluated because they can negatively affect adherence to the treatment despite once-daily dosing [26].

Despite the evidence provided by this study, some limitations should be considered. One of the most important ones is that a limited number of studies were included in this analysis, which limits the generalizability and applicability of the study. Furthermore, no studies have compared this drug with other antihypertensive agents such as Calcium Channel Blockers (CCBs) or other combination pills. Another limitation is that the dose cannot be adjusted for the individual drugs in combination.

Given the results witnessed from this meta-analysis for the use of the N/V combined pill, there is a need for more high-quality RCTs to investigate the long-term effects of the pill, specifically in diverse patient populations. Also, future studies must address the limitations and gaps acknowledged in this analysis, such as the necessity for gender-specific analyses and data on patients' comorbidities. Furthermore, studies focusing on the probable adverse effects and the safety profile of the N/V combined pill are essential to warrant broader clinical use.

This meta-analysis exhibits the advantage of the N/V combined pill to decrease SBP as opposed to nebivolol or valsartan monotherapy. Despite a few limitations, these findings deliver a solid basis for considering such a combination therapy for the management of hypertension, especially among those patients who may not be able to achieve sufficient blood pressure control with monotherapy. Future studies should be conducted to confirm these results in much larger and more diverse populations while also exploring this treatment approach's long-term efficacy and safety.

Conclusion

The present meta-analysis demonstrated that the N/V combined pill effectively reduces central SBP and DBP in hypertensive patients compared to monotherapy with either nebivolol, valsartan, or valsartan/amlodipine combination. The combination pill treatment markedly decreased SBP and showed mild effectiveness in DBP outcomes; however, no statistically significant difference was seen compared to valsartan/amlodipine combos. Despite concerns over renin suppression overlap, the N/V combined pill was generally well tolerated, with no significant safety issues observed. However, the studies included were missing long-term data and exhibited minimal variety in patient groups, limiting the overall quality of evidence. In addition, the N/V combination needs to be evaluated in hypertensive individuals, especially those with supplementary cardiac risks; however, further research involving larger sample sizes, varied demographics, and prolonged follow-up durations is essential to confirm its long-term efficacy and safety profile.

Declarations

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Declaration of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data statement: Research data is available from the corresponding author upon reasonable request.

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