Drug Corner

Hypertension Therapeutics Reimagined : Nebivolol and Telmisartan — A Contemporary Review

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Hypertension, a prevalent Global health concern, affects a quarter of the population, with an increasing incidence among young adults. In India, approximately 27 million young adults grapple with hypertension but awareness, treatment, and control remain low. Early-onset hypertension significantly elevates cardiovascular risks in later life, necessitating a paradigm shift in management approaches. The combination of nebivolol, a third-generation ß1-selective ß-blocker and telmisartan, an Angiotensin Receptor Blocker (ARB), emerges as a promising therapeutic strategy. The complementary mechanisms of these drugs on the Sympathetic Nervous System (SNS) and the Renin-angiotensin-aldosterone System (RAAS) prove crucial for robust Blood Pressure (BP) control and cardiovascular risk reduction. Nebivolol's unique vasodilatory effects, minimal metabolic impact, and telmisartan's distinct pharmacokinetic properties present complementary mechanisms for BPcontrol. Various clinical trials underscore the efficacy of this combination in reducing mean systolic and diastolic BP, heart rate and cardiovascular events.This review also highlights the potential benefits of combination therapy in populations with comorbidities such as obesity, insulin resistance, dyslipidemia, asthma, Chronic Obstructive Pulmonary Disease (COPD) and Erectile Dysfunction (ED). Furthermore, the additive effects of nebivolol and telmisartan, as well as the reduced pill burden through fixed-dose combinations, enhance patient adherence and overall hypertension management. In conclusion, the nebivolol and telmisartan combination provides a holistic and promising approach to hypertension management, emphasising the need for continued research to uncover its long-term benefits and broaden its application in tailored treatment strategies for hypertension in young adults.

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Hypertension, a major risk factor for all-cause mortality, morbidity and cardiovascular disease, affects one-quarter of the Global population and is common among young people, affecting 1 in 8 adults aged between 20-40 years. India, with 32% of its 1.2 billion people being young adults according to the 2011 census, assumes a prevalence rate of around 27 million young adults with hypertension. The awareness, treatment and control of high BP among young adults with hypertension are notably low and pre-hypertension serves as a significant precursor for developing hypertension and CV disease later in life. Despite this, there is a lack of screening for pre-hypertension and hypertension among young individuals and healthcare professionals are less likely to prescribe anti-hypertensive drugs to young adults with hypertension compared to older patients. Previously, age has been a significant factor in treatment decisions, emphasising those with the highest 10-year risk of CV events, but young hypertension increases the risk of CV events in middle age, contributing to the earlier development of heart failure, coronary heart disease, transient ischemic attacks and stroke. Although good national guidelines exist, they do not serve low-risk young hypertensive patients as effectively as older patients[1-3].

Hypertension, even in young adults, can have harmful health effects and is associated with higher rates of left ventricular hypertrophy and changes in brain volume and white matter hyperintensity volume. Studies such as the Strong Heart Study and the Coronary Artery Risk Development in Young Adults (CARDIA) longitudinal study emphasise the importance of early-life risk factors.In the Strong Heart Study, 1940 Native Americans aged 14 to 39 years were examined for clinical and echocardiographic features and showed higher rates of left ventricular hypertrophy in individuals with pre-hypertension (blood pressure120-139/80-89mmHg) and hypertension (blood pressuree ≥140/90 or taking antihypertensive medications) compared to those with normotensive individuals of the same age[1,4]. The CARDIA longitudinal study, which included a cohort of 5115 young adults aged 18 to 30 years, demonstrated that elevated SBP at baseline predicted the presence of coronary artery calcium 15 years later and emphasised the role of early-life risk factors in the development of coronary

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heart disease in later life. Moreover, a retrospective analysis of CARDIA data demonstrated that individuals under 40 years old at baseline who had hypertension as defined by the 2017 ACC/AHA guidelines had a significantly higher risk of CV disease compared to those with normal blood pressure (<120/80mmHg)[5,6].

Despite significant progress in understanding the complex pathophysiological mechanisms of hypertension, lowering BP through the use of all major antihypertensive drug classes Angiotensin-converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs), ß-blockers, calcium channel blockers (CCBs) and diuretics)remains the best strategy to reduce cardiovascular risk associated with hypertension. According to the most recent international ESC/ESH guidelines, ß-blockers maintain a central role in the management of hypertension, being recommended at any treatment step when there is a specific indication, such as heart failure, angina, post-acute myocardial infarction, atrial fibrillation or pregnancy. In particular, nebivolol, a third-generation ß1-selective ß-blocker, has demonstrated advantages over other ß-blockers, including vasodilatory properties, neutral metabolic effects and good tolerability, making the drug suitable for a wide range of hypertensive patients with or without co-morbidities[7,8].

Around 75% of hypertensive patients require combination therapy for BP control due to multiple pathophysiological pathways and counter regulatory responses. In India, dual and triple therapies often involve ARBs with telmisartan being a preferred choice among physiciansdue to its sustained effectiveness, morning BP surge control and its role in preventing complications like microalbuminuria, nephropathy, cardiovascular morbidity and mortality. A cross-sectional observational survey conducted by Jadhav U, *et al* using a structured questionnaire showed that among young hypertensive patients, ARBs and beta-blockers were the preferred drug classes, with 61.6% choosing ARBs and 15.8% opting for beta-blockers (Fig 1). Calcium channel blockers, diuretics and ACE inhibitors were selected by 10.4%, 7.6%, and 4.6% of respondents, respectively[9,10]. Combining anti-hypertensive drugs with complementary mechanisms of action enhances efficacy, reduces side effects, and provides a broader approach to blood pressure control through additive drug effects[11]. This review delves into the mechanisms, clinical evidence and potential benefits of this synergistic combination, highlighting its advantages over individual use.

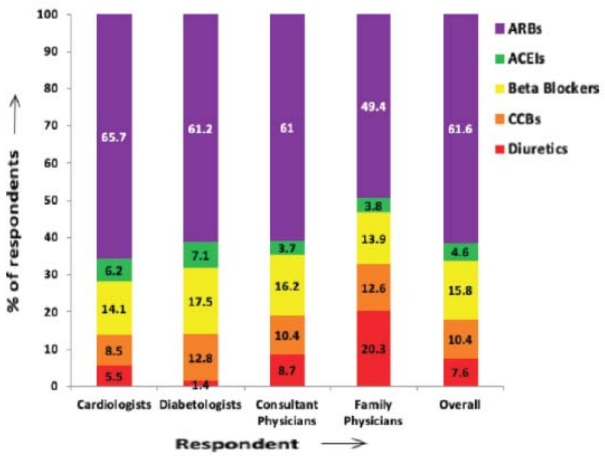

Fig 1 — Drug class preference for the management of hypertension in young adults

Complimentary Action of SNS and RAAS : A Duet of Mechanisms

The combination of Nebivolol (ß-blockers) and Telmisartan (ARBs) offers distinct and complementary mechanisms for controlling BP and is of particular interest due to their complementary effects on the Renin-angiotensin-aldosterone System (RAAS) and the Sympathetic Nervous System (SNS), two interconnected pathways that affect cardiovascular risk and disease outcomes.

Nebivolol, a third-generation $ß_1$ adrenoreceptor antagonist, exhibits unique characteristics, including Nitric Oxide (NO)-mediated vasodilation through $ß_3$ receptor agonism and reduced oxidative stress, distinguishing it from conventional non-vasodilatory ß-blockers such as atenolol as well as from vasodilatory ß-blockers like carvedilol and labetalol, which act through α_1 adrenergic antagonism. It also offers a better tolerability profile and reduced metabolic effects, along with aldosterone reduction for potential blood pressure control[9,11].

The renin-angiotensin system plays a crucial role in blood pressure regulation and volume homeostasis. The angiotensin receptor blockers control high blood pressure by blocking the binding of angiotensin II to the angiotensin subtype 1 receptor, which is believed to be responsible for the majority of the physiologic actions of angiotensin II relevant to the regulation of blood pressure. Telmisartan, a widely used ARB, possesses distinct pharmacokinetic and pharmaco-dynamic properties, including partial Peroxisome Proliferator-activated Receptor (PPAR)γ agonism and a long duration of action.Telmisartan has a higher affinity for the angiotensin type 1 receptor (more than 3000 times) than the angiotensin type 2 receptor,

potentially allowing angiotensin II to have beneficial effects via this receptor. This could lead to increased bradykinin production, vasodilation, andendothelial dysfunction. Nebivolol may counter-regulate this increase in renin, allowing a dual RAAS blockade. ARBs may also lead to a reactive increase in aldosterone caused by angiotensin II blockade, which could potentially be mitigated with combination therapy, resulting in improved efficacy[9,12].

Cardiovascular (CV) Benefits : Insights from Clinical Trials and Studies

Guideline Evolution on Combination Therapy:

According to epidemiological data, BP reduction at the population level is beneficial. The careful monitoring of BP from early adulthood to later life and the detection of cardiovascular and brain changes in young adults with hypertension support the argument that young people with high BP should be treated in the same way as older adults. However, there is a lack of data assessing pharmacological intervention in this young age group[1]. There is now general agreement that monotherapy is less likely to be adequate to achieve optimal BP control in the majority of patients and combination therapy involving two or more anti-hypertensive drugs is typically necessary for targeted BP accomplishment and CV risk reduction. Moreover, according to JNC 7 guidelines and the guidelines put forth jointly by the International Society of Hypertension and the European Society of Hypertension, BP-lowering treatment should be initiated with a combination of two drugs in patients with multiple CV risk factors such as metabolic syndrome, diabetes and heart and renal disease, as well as in patients with a systolic pressure higher than 20 mmHg and/or diastolic pressure higher than 10 mmHg of the targeted goal[13].

Effects on Blood Pressure (BP) :

The Giles, *et al* study demonstrated that nebivolol monotherapy is an effective and well-tolerated treatment option for the phenotype of a younger adult with diastolic hypertension, a patient population that is often overlooked. Furthermore, a high proportion of patients with a Diastolic Blood Pressure (DBP) reduction $\geq$8 mm Hg is encouraging because DBP is a stronger predictor of coronary heart disease than SBP or pulse pressure in individuals younger than 50 years[14].

Another study conducted by Sharpe M, *et al* demonstrated that telmisartan is an effective anti-hypertensive agent that significantly reduces blood pressure in patients with mild to moderate hypertension, with maximum reduction observed at a dosage of 40 to 80 mg/day. Telmisartan is associated with a significantly lower incidence of dry, persistent cough compared to lisinopril and is comparable in efficacy to other major classes of antihypertensive agents, such as amlodipine, atenolol, enalapril and lisinopril. Thus, for the treatment of hypertensive patients, telmisartan is a valuable therapeutic choice.[15]

Effects on Heart Rate (HR) :

The BENEFIT KOREA study, led by Jinho S, *et al* demonstrated that once-daily nebivolol, either as monotherapy or add-on therapy, significantly reduced mean SBP and DBP in 3011 adult South Korean patients with essential hypertension with or without co-morbidities. Additionally, a significant decrease in HR was also noted. The reductions in SBP and DBP were significantly greater when nebivolol was used as monotherapy in de novo patients and as add-on therapy to existing anti-hypertensives (angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers)[16].

The VALUE trial demonstrated that elevated heart rate is an important factor in cardiovascular risk even when individual BP is well controlled,suggesting that both BP and heart rate must be lowered for optimal risk reduction. Elevated heart rate is now recognised as a key variable influencing cardiovascular risk in hypertension patients and provides a strong rationale for the use of interventions that target heart rate by modulating the SNS. In combination therapy, a beta-blocker component is essential to achieve optimal control caused by sympathetic overdrive, particularly with a selective beta-1 blocker, preserving beta-2-mediated vasodilation, inhibiting sympathetic activity in the heart and kidney and minimising adverse effects associated with beta-2 receptor blockade in the lungs and peripheral tissues[17].

Effects on Left Ventricular Hypertrophy (LVH) :

Left Ventricular Hypertrophy (LVH) is a risk factor for cardiovascular mortality and morbidity and its regression is important for patient outcomes.In a study involving controlled hypertensive patients with Left Ventricular Hypertrophy (LVH), Fountoulaki, *et al* compared the effects of nebivolol (2.5-5 mg) and telmisartan (40-80 mg) on Blood Pressure (BP) control and Left Ventricular Mass (LVM). Both groups exhibited similar reductions in BP and a 14g/m^2 decrease in LVM, possibly due to different mechanisms[18].

Degirmenci, *et al* conducted a prospective cohort study to assess the long-term effects of irbesartan, an ARB and new-generation beta-blockers (such as nebivolol and carvedilol) on LVH associated with essential hypertension. The results showed that both

new-generation beta-blockers were more effective than irbesartan in the regression of LVH, with notable improvements observed 3 months after nebivolol treatment and 6 months following irbesartan and carvedilol treatments[19]. In a study by Misra, *et al* telmisartan proved to be more effective than atenolol in achieving LVH regression, resulting in a substantial 27.49% reduction in Left Ventricular Mass Index (LVMI) with a higher proportion of patients achieving the target LVMI value[20].

Effects on Cardiovascular (CV) Protection :

Elevated SBP or DBP increases cardiovascular risk and even small reductions in severe hypertension can have a significant positive impact. The ONTARGET study showed that the ARB telmisartan preserved 95% of the vascular protective properties of the ACE iramipril when administered at similar doses to a similar patient group. The TRANSCEND study demonstrated benefits in a patient in tolerant to ACEi, with a trend towards a combined secondary end point of cardiovascular death, MI and stroke. Despite the primary endpoint being neutral, with excellent tolerance of the ARB,the reductions in the risk of stroke, myocardial infarction, and CV death were 19%, 14% and 35%, respectively. These studies suggest that an ARB can be used as an alternative to an ACEi for vascular protection in high-risk individuals. For individuals with a high risk of cardiovascular disease, telmisartan is the only ARB that has been demonstrated to reduce cardiovascular risk[12,21].

The INTERHEART study revealed that hypertension increases the risk of a myocardial infarction by 25%. Lowering BP has a positive impact on myocardial infarction risk, with a 17% reduction in Coronary Artery Disease (CAD) for every 10 mmHg reduction in SBP, as evidenced by a recent meta-analysis of Randomised Controlled Trials (RCTs) of anti-hypertensive therapy. In hypertensive patients with CAD, the preferred components of the antihypertensive drug treatment strategy are ß-blockers, either in combination with blockers of the Renin-angiotensin System (RAS) or CCBs[8].

Effects on Mortality :

The European Trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease (EUROPA), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trials demonstrated that the addition of RAAS inhibitors to a preexisting ß-blocker treatment resulted in a 20% reduction in the relative risk of the primary end point, a 23% reduction in non-fatal myocardial infarction, and a 22% reduction in all-cause mortality compared to placebo[22]. Nebivolol significantly reduces all-cause mortality or cardiovascular hospitalisation compared to placebo,as reported by the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS)[8].

Dual-Class Indications :

Nebivolol and telmisartan may be beneficial for patients with indications for both drug classes. While nebivolol is not a first-line option for HTN, it may be considered for specific populations, like post-myocardial infarction patients. In individuals with metabolic syndrome or diabetes requiring a ß-blocker, nebivolol's metabolically neutral profile might offer benefits over other ß-blockers. For patients with chronic kidney disease or diabetes who are unable to tolerate ACE inhibitors, the nebivolol/telmisartan combination becomes a favourable option[9].

Hypertension with Comorbidities :

Obesity :

Obesity-related hypertension involves multiple systems, such as the SNS and the RAAS. Lifestyle changes alone may not be enough to control BP. A study by Manrique C, *et al* examined the effects of nebivolol, a β-blocker, on blood pressure control in obese and non-obese hypertensive patients. Nebivolol significantly lowered diastolic blood pressure in both groups and systolic blood pressure in non-obese patients. The drug also had neutral effects on lipid and carbohydrate metabolism, making it apotential option for controlling blood pressurein moderately obese individuals[23]. Another post hoc analysis by Mende C, *et al* found that a Single-pill Combination (SPC) of nebivolol (ß-blocker) and valsartan (ARBs) is effective in lowering BP in individuals regardless of their obesity status. This combination significantly lowered blood pressure and aldosterone levels in both obese and nonobese participants compared to placebo and was more effective than nebivolol or valsartan monotherapies.[24]

Insulin Resistance, Lipid Profile and Dyslipidemia:

Many antihypertensive medications negatively impact metabolism, making blood pressure control difficult in hypertensive patients with metabolic abnormalities. Nebivolol, a third-generation vasodilatory β-blocker, significantly lowers blood sugar, HbA1c, total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol compared to atenolol and improves serum lipid profile and glycemic control[25].

Telmisartan, compared to other ARBs, is superior in improving insulin resistance, reducing fasting insulin and fasting blood glucose, decreasing diastolic blood pressure and significantly reducing serum triglycerides, VLDL-C, LDL-C and cholesterol levels while increasing HDL-C levels in hypertensive patients with dyslipidemia. Furthermore, in these patients, telmisartan effectively reduced both systolic and diastolic blood pressure[26].

Asthma and/or Chronic Obstructive Pulmonary Disease (COPD) :

Beta-blockers are recommended for COPD patients due to their cardio-protective properties, lower heart rate and improved systolic function. However, they are underutilised in heart failure and post-myocardial infarction due to concerns about bronchoconstriction, even with cardio-selective drugs. Retrospective observational studies have demonstrated significant reductions in exacerbations and mortality conferred by beta-blockers in COPD. Beta-1-selective antagonists such as bisoprolol, nebivolol and metoprolol are preferred over non-selective carvedilolas they are less likely to cause broncho-constriction in COPD patients.Studies have shown that nebivolol exhibits greater in vitro beta-1/2 receptor selectivity and suppresses endothelial nitric oxide more effectively than bisoprolol in the human myocardium[27].

For patients with asthma and hypertension, ARBs may be the preferred drugs that act on the renin-angiotensin system. In patients with severe asthma during exacerbations, levels of circulating angiotensin II and renin were found to be increased as compared with those without exacerbations.Inhibition of angiotensin II type 1 receptors has led to a slight decrease in bronchial hyperresponsiveness.ARBs target pathways that can address both hypertension and asthma without inducing coughing, making them safe for patients with asthma or COPD. In a small trial, ARBs were found to be well tolerated and did not increase cough or bronchial hyperreactivity in hypertensive patients with asthma, similar to calcium channel blockers[28].

Erectile Dysfunction (ED) :

Beta-blockers are linked to Erectile Dysfunction (ED), which is more common in men with hypertension. Compared to other beta-blockers, nebivolol, a beta-blocker with vasodilating properties, may offer an advantage in improving erectile function. The study conducted by Sharp, *et al* found that when a practitioner specifically wants to use a beta blocker as an add-on antihypertensive treatment, nebivolol may be useful in patients who have or are at risk of developing ED[29].

Additive Effect :

Combining antihypertensive drugs can be more effective than increasing monotherapy doses for treating hypertension. Current guidelines have recognized this and provided enhanced support for initial combination therapy in hypertensive patients, although it has been limited by patient compliance and cost.The combination of ß-blockers and RAAS inhibitors has been deemed 'less effective' due to partially overlapping mechanisms of action and limited evidence.A randomized Phase 3 trial (NAC-MD-01; 4161) has provided convincing evidence that at least one ß-blocker/RAAS inhibitor combination, comprising the $ß_1$-selective adrenergic blocker with agonistic vasodilatory properties, Nebivolol,and the $ß_3$ Angiotensin II Receptor Blocker (ARB), valsartan, is more effective in reducing BP than their monotherapies. Based on the results of this study, the US Food and Drug Administration has approved the 5/80-mg/day Neb/valsartan Single-pill Combination (SPC) for hypertension treatment[30].

Combining drugs with different, yet complementary, mechanisms of action is the most effective approach for achieving additive BP-lowering effects. However, it is important to note that not all combinations of drugs from complementary drug classes produce strong additive effects. In a study conducted by Ishak, *et al* the combination of a specific ß-blocker (nebivolol) and RAAS inhibitor (valsartan) demonstrated additive effects, which may be attributed to the multi-modal effects of nebivolol, making it unique from other ß-blockers. Nebivolol has a better tolerability profile than other ß-blockers, which may be explained by differences in receptor affinity and vasodilatory pathways and may also explain why the ß-blocker nebivolol/RAAS inhibitor combination has demonstrated greater additivity than other non-vasodilatory or non-$ß_1$-selective ß-blocker and RAAS inhibitor combinations in previous hypertension trials[11].

Fixed-Dose Combination Reduces Pill Burden :

In addition, combination antihypertensives can increase adherence by decreasing pill burden and dosing frequency, resulting in improved HTN management and subsequent patient outcomes. According to one meta-analysis, a 26% improvement in adherence was found with single-pill combination antihypertensives, especially if this is accomplished cost-effectively[9]. ß-blocker nebivolol and ARB telmisartan reduce BP through complementary mechanisms. When used in combination, their efficacy surpasses that of component monotherapies[30].

Conclusion :

Hypertension among young adults is a significant health concern with long-term implications for cardiovascular health and the synergistic combination of nebivolol and telmisartan emerges as a promising strategy for its management. The dual action of the SNS and the RAAS contributes to robust blood pressure control, cardiovascular protection, and reduced left ventricular hypertrophy. The benefits extend to specific populations, including those with comorbidities, showcasing the versatility of this combination. Notably, the combination's efficacy, tolerability and potential to reduce pill burden underscore its clinical significance. However, further research is warranted for comprehensive validation of long-term outcomes and safety profiles in diverse patient cohorts. Overall, the combination of nebivolol and telmisartan represents a promising and personalized approach to hypertension, addressing the complex interplay of physiological pathways associated with cardiovascular health.

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References

1 Hinton TC, Adams ZH, Baker RP — Investigation and Treatment of High Blood Pressure in Young People: Too Much Medicine or Appropriate Risk Reduction? *Hypertension* 2020; **75(1):** 16-22.
2 Geevar Z, Krishnan MN, Venugopal K — Prevalence, Awareness, Treatment, and Control of Hypertension in Young Adults (20-39 Years) in Kerala, South India. *Front Cardiovasc Med* 2022; **18;9:** 765442.
3 Meher M, Pradhan S, Pradhan S — Risk Factors Associated With Hypertension in Young Adults: A Systematic Review. *Cureus* 2023; **15(4):** e37467.
4 Drukteinis JS, Roman MJ, Fabsitz RR — Cardiac and systemic hemodynamic characteristics of hypertension and prehypertension in adolescents and young adults: the Strong Heart Study. *Circulation* 2007; **115:** 221-7.
5 Yano Y, Reis JP, Colangelo LA — Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life. *JAMA* 2018; **320(17):** 1774-82.
6 Loria CM, Liu K, Lewis CE — Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA Study. *J Am Coll Cardiol* 2007; **49(20):** 2013-20.
7 Williams B, Mancia G, Spiering W — 2018 ESC/ESH guidelines for the management of arterial hypertension. J Hypertens 2018; **36:** 1953-2041.
8 Ferri C — The role of nebivolol in the management of hypertensive patients: from pharmacological profile to treatment guidelines. *Future Cardiol* 2021; **17(8):** 1421-33.
9 Battise D, Boland CL, Nuzum DS — Nebivolol/Valsartan: A Novel Antihypertensive Fixed-Dose Combination Tablet. *Annals of Pharmacotherapy* 2019; **53(4):** 402-12.
10 Jadhav U, Tiwaskar M, Khan A — Hypertension in Young Adults in India: Perspectives and Therapeutic Options amongst Clinician's in a Cross Sectional Observational Study. *J Assoc Physicians India* 2021; **69(11):** 11-2.
11 Ishak J, Rael M, Punzi H — Additivity of nebivolol/valsartan single-pill combinations versus other single-pill combinations for hypertension. *J Clin Hypertens* 2018; **20:** 14-9.
12 Unger T, Schupp M — Telmisartan: from lowering blood pressure to end-organ protection. *Future Cardiol* 2005; **1(1):** 7-15.
13 Varagic J, Punzi H, Ferrario CM — Clinical utility of fixed-dose combinations in hypertension: evidence for the potential of nebivolol/valsartan. *Integr Blood Press Control* 2014; **7:** 61-70.
14 Giles TD, Khan BV, Lato J — Nebivolol monotherapy in younger adults (younger than 55 years) with hypertension: a randomized, placebo-controlled trial. *J Clin Hypertens (Greenwich)* 2013; **15(9):** 687-93.
15 Sharpe M, Jarvis B, Goa KL — Telmisartan: a review of its use in hypertension. *Drugs* 2001; **61(10):** 1501-29.
16 Shin J, Choi YJ, Hong GR — Real-world efficacy and safety of nebivolol in Korean patients with hypertension from the BENEFIT KOREA study. *J Hypertens* 2020; **38(3):** 527-35.
17 Strauss MH, Hall AS, Narkiewicz K — The Combination of Beta-Blockers and ACE Inhibitors Across the Spectrum of Cardiovascular Diseases. *Cardiovasc Drugs Ther* 2023; **37(4):** 757-70.
18 Fountoulaki K, Dimopoulos V, Giannakoulis J — Left ventricular mass and mechanics in mild-to-moderate hypertension: effect of nebivolol versus telmisartan. *Am J Hypertens* 2005; **18:** 171-7.
19 Degirmenci H, Açikel M, Bakirci EM — Comparison of effects of nebivolol, carvedilol and irbesartan on left ventricular hypertrophy associated with hypertension. *Eur Rev Med Pharmacol Sci* 2014; **18(5):** 630-7.
20 Misra KH, Das MC, Ramani YR — Effect of telmisartan on the regression of the left ventricular hypertrophy in the patients of essential hypertension. *J Clin Diagn Res* 2013; **7(7):** 1352-5.
21 Fitchett D — Results of the ONTARGET and TRANSCEND studies: An update and discussion. *Vascular Health and Risk Management* 2009; **5:** 21-9.
22 Brugts JJ, Bertrand M, Remme W — The treatment effect of an ACE-inhibitor based regimen with perindopril in relation to beta-blocker use in 29,463 patients with vascular disease: a combined analysis of individual data of ADVANCE, EUROPA and PROGRESS trials. *Cardiovasc Drugs Ther* 2017; **31(4):** 391-400.
23 Manrique C, Whaley-Connell A, Sowers JR — Nebivolol in obese and non-obese hypertensive patients. *J Clin Hypertens (Greenwich)* 2009; **11(6):** 309-15.
24 Mende CW, Giles TD, Bharucha DB — Efficacy of nebivolol-valsartan single-pill combination in obese and nonobese patients with hypertension. *J Clin Hypertens (Greenwich)* 2017; **19(6):** 632-639.
25 Majid A, Javed A, Hussain M — Effect of nebivolol beneficial on lipid profile and glycemic control in comparison with Atenolol in patients with type 2 DM with concomitant hypertension. *Pak J Pharm Sci* 2021; **34(5(Supplementary):** 1891-5.
26 Wang Y, Qiao S, Han DW — Telmisartan Improves Insulin Resistance: A Meta-Analysis. *Am J Ther* 2018; **25(6):** e642-e651.
27 Lipworth B, Wedzicha J, Devereux G — Beta-blockers in COPD: time for reappraisal. *Eur Respir J* 2016; **48(3):** 880-8.
28 Christiansen SC, Zuraw BL — Treatment of Hypertension in Patients with Asthma. *N Engl J Med* 2019; **381(11):** 1046-57.
29 Sharp RP, Gales BJ — Nebivolol versus other beta blockers in patients with hypertension and erectile dysfunction. *Ther Adv Urol* 2017; **9(2):** 59-63.
30 Giles TD, Cockcroft JR, Pitt B — Rationale for nebivolol/valsartan combination for hypertension: review of preclinical and clinical data. *J Hypertens* 2017; **35:** 1758-67.