



EFFECT OF BETA BLOCKER ON VASCULAR FUNCTION IN SYSTEMIC HYPERTENSION

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Abstract

The contribution of beta-blockers in the management of hypertension has been overhauled and is currently used as a secondary treatment with results trials on the traditional methods such as atenolol. This paradigm shift is due to a vascular-centric concept of hypertension in which successful therapy is necessary to reverse endothelial dysfunction, vascular remodeling, and arterial stiffness, which are the underlying causes of cardiovascular risk. The conventional, beta-blockers that decrease blood pressure by decreasing cardiac output merely fail to increase these vascular parameters and may negatively influence central hemodynamics and metabolism, which explains why they are inferior in stroke prevention. More importantly, the beta-blocker group is a pharmacologically heterogeneous group. Some third-generation vasodilating beta-blockers (e.g., nebivol, carvedilol) have different mechanisms, one of nitric oxide potentiation, α_1 -adrenergic inhibition, and antioxidant effects, directly aimed at vascular pathophysiology. It has been shown that these agents enhance endothelial performance and decrease the arterial stiffness in a better way in comparison with the traditional beta-blockers with a better metabolic and hemodynamic profile. As such, blanket declassification of all beta-blockers is no longer relevant. The individualized, pathophysiology-oriented approach is justified. Beta-blockers that dilate the vas are a logical choice in patients with hypertension who have a high sympathetic tone, metabolic syndrome, or particular comorbidities, and a therapeutic objective of obtaining vascular protection. Guidelines and clinical practice in the future ought to make a differentiation between the subclasses of beta-blockers, taking advantage of their distinct vascular advantages.

Keywords: Hypertensive vasculature, Beta-blockers, Vascular dysfunction, Endothelial function, Arterial stiffness, Vasodilating beta-blockers

Introduction

Hypertension is the most important risk factor that can be modified to cause cardiovascular morbidity and mortality across the world with more than a billion affected persons. Its insidious load is far beyond high brachial cuff measurements and it is a vasculature disease systemic in nature, the cause of end-organ injury[1]. Pervasive vascular dysfunction is the primary pathology underlying this cascade and a maladaptive process that is based on endothelial lining, vascular smooth muscle and extra-cellular matrix. Originally, endothelial dysfunction, which is defined as a reduction in the nitric oxide (NO) bioavailability, as well as the elevation of oxidative stress and a pro-inflammatory environment, impairs vasodilation and leads to the development of a thrombotic environment[2][3]. This steps up to structural changes: hypertrophic remodelling of resistance vessels and augmentation of inflexibility of elastic conduits through growing of vascular smooth muscle cells, depositing collagen and fragmenting elastin. As a result, the vasculature becomes a

stature instead of being a responsive and dynamic conduit, raising central aortic pressure, compromising coronary perfusion, and raising cardiac afterload[4]. This is the last vascular pathology that leads to disastrous events such as stroke, myocardial infarction and heart failure as well as chronic renal impairment[5]. Hence, the effectiveness of any antihypertensive treatment should not be evaluated only on whether it can reduce peripheral systolic and diastolic parameters, but its ability to stop or reverse such underlying vascular abnormalities. This vascular-based approach is essential to consider the role of beta-adrenergic receptor blockers (beta-blockers), in the category of which, the therapeutic status of this drug group has been controversially transformed[6][7]. Previously one of the pillars of antihypertensive management, beta-blockers have seen a major paradigm shift in key international guidelines and are no longer considered first-line agents, but rather a more niche agent[8][9]. The key trials that led to this demotion included the Anglo-Scandinavia Cardiac outcomes trial (ASCOT-BPLA) that proved that an atenolol based regime was worse than an amlodipine based regime in the prevention of major cardiovascular events, especially stroke in the face of comparable brachial blood pressure management[10]. Such fears were subsequently substantiated by other meta-analyses, which indicated that at an equivalent drop in brachial pressure, beta-blockers (in particular, non-vasodilating agents such as atenolol) were associated with a greater risk of stroke than other medication groups[11]. The given reasons are adverse effects on central aortic hemodynamics (inability to decrease central systolic pressure in an equal measure with brachial pressure), metabolic malfunctions (e.g., dysglycemia, dyslipidemia), and low tolerability[12]. As a result, the beta-blockers are currently recommended as the first-line treatment to hypertensive patients with strong proving evidence including cases of heart failure of reduced ejection fraction, post-myocardial infarction, or atrial fibrillation that necessitates rate-control. In simple hypertension the medications are usually used as a fourth-line add-on treatment[13][14]. Their major hemodynamic advantage in hypertension was attributed in the past to a decrease in cardiac output through chronotropy and inotropy. But this same mechanism may reveal, or also may not attenuate peripheral vascular resistance sufficiently[15]. Non-selective or high-dose β_1 -selective agents can do so, leaving α_1 -adrenergic vasoconstrictor tone unopposed by blocking a vascular β_2 -adrenergic receptor, which normally mediates vasodilation, so that peripheral vasoconstriction can occur, or, at best, α_1 -adrenergic agents will have neutral direct vascular effects[16][17]. Moreover, a decreased cardiac output may result in compensatory neurohumoral responses, such as heightened peripheral resistance, which may have a suppressed blood pressure control over time. This brings a paradox; the same drug will, although acting by central cardiac processes, elevate the blood pressure may also have a neutral or even deleterious direct effect on the diseased vasculature itself[18]. Such a lack of local vascular effect coupled with systemic hemodynamic advantage is postulated to be the cause of their poor performance in stroke prevention -an event that is highly sensitive to arterial stiffness and pulsatile loading- in comparison to treatments such as calcium channel blockers or renin-angiotensin system inhibitors, which are direct vasodilators and have more favourable effects on arterial stiffness and wave reflections. The knowledge void that needs to be bridged thus is the one that shifts the current monolithic understanding of the beta-blockers as a group to a more vascular-focused re-conceptualization that is sensitive to the pharmacological heterogeneity inherent to these agents[19]. The class is not homogenous; these agents include cardioselective (β_1), intrinsic sympathomimetic activity (ISA), and most crucial in vascular activity, agents with ancillary vasodilating activity. Third-generation vasodilating beta-blockers (nebivolol, which activates endothelial NO synthase via β_3 -adrenergic receptor agonism and carvedilol, which blocks α_1 -adrenergic receptors and has antioxidant properties) have entirely different vascular actions than their predecessors[20][21]. It is emerging that these agents can enhance the functioning of the endothelium, decrease the stiffness of arteries, as well as have anti-inflammatory and antioxidant properties in the vessel wall-functions that are consistent with the modern aim of vascular protection. Therefore, the dominant narrative of guideline that was mostly developed through the experiment with atenolol might become outdated in the case of the overall pharmacologic group[21][22]. There should be a more detailed

reevaluation to unravel how the various beta-blocker subtypes directly and indirectly affect the pillars that constitute hypertensive vascular disease endothelial dysfunction, remodeling, and stiffness. This kind of analysis would be fundamental in informing personalized therapy that may reclaim the role of certain beta-blockers to hypertensive phenotype of high sympathetic drive, select comorbidities or as part of customized combination protocols of actual vascular restoration[23].

The Hypertensive Vasculature: Pathophysiology as a Therapeutic Target

The pathophysiology of the hypertensive vasculature is a complex sequence of events, the functional dysfunction of which inevitably develops into structural dysfunction. Endothelial dysfunction, the key triggering event of this process, occurs at the epicenter of the process predisposing the development of long-term vascular damage[24]. The healthy endothelium through the enzymatic activity of endothelial nitric oxide synthase (eNOS) has a continuous production of nitric oxide (NO), a powerful vasodilator, anti-inflammatory, anti-thrombotic, and anti-proliferative agent[25]. In hypertension, this defense system is extremely derailed. This is caused by chronic pressure overload and the related metabolic insults which cause the eNOS to become uncoupled, i.e., the enzyme produces reactive oxygen species (ROS), especially superoxide anion (O_2^-), rather than NO. The increased oxidative stress is also enhanced by the upregulation of NADPH oxidases (Nox) and dysfunction of mitochondria[26]. The ensuing superoxide quickly removes the already reduced NO to create peroxynitrite ($ONOO^-$), which is a greatly harmful molecule that further oxidizes the essential eNOS cofactor tetrahydrobiopterin (BH_4), and this then feeds forward on the uncoupling cycle in a vicious cycle. This leads to the death of NO bioavailability. At the same time, the inflamed endothelium enhances the synthesis of strong vasoconstrictors such as endothelin-1 (ET-1) and expression of adhesion molecules (VCAM-1, ICAM-1) that facilitate leukocyte infiltration[27][28]. This produces a pro-inflammatory, pro-contractile and pro-thrombotic condition that is the pathophysiological signature of the hypertensive vessel and is vulnerable to vasospasm, atherosclerosis, and ischemia.

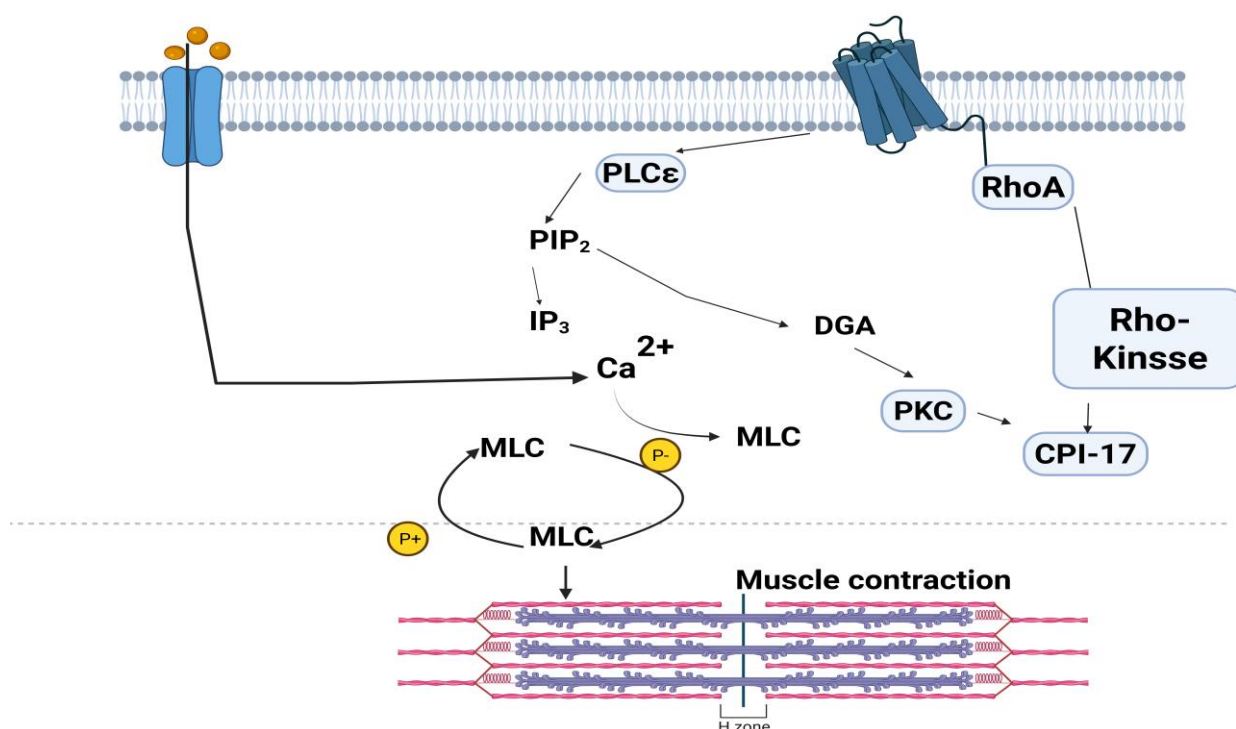


Fig: 1 Signal Transduction Pathway Leading to Muscle Contraction

This pathological signaling environment leads to vascular remodeling and subsequent stiffening, and transforms a reactive into a structural fixed anomaly with time. The phenotypic transition of vascular smooth muscle cells (VSMCs) is caused by the loss of NO as a growth inhibitor, the mitogenic effect of angiotensin II, endothelin-1, and enhanced mechanical stress. The cells become

a synthetic, proliferative and migratory cell type, as opposed to being in a contractile and quiescent phase[29]. They hypertroph and hyperplastic and invade the lumen of the vessels (eutrophic and hypertrophic remodeling), and thus augment peripheral resistance. At the same time, these stimulated VSMCs, and inflammatory cells and fibroblasts, radically modify the extracellular matrix (ECM) composition. The stiff collagens (type I, type III) are overdeposited and the flexible elastin fibers are enzymatically degraded by the matrix metalloproteinases (MMPs) and fragmented[30]. This change in the collagen-elastin ratio, and more complex glycated end-products (AGE) cross-linking of matrix proteins, are fundamental to alter the material properties of the arterial wall. The conduit arteries and especially the aorta and its great vessels lose their Windkessel compliance -their capacity to absorb the pulsatile cardiac propulsion. This causes further stiffening of the arteries which is a potent independent predictor of heart deaths[31][32]. Its hemodynamic result is an increase in central aortic systolic and pulse pressures, an increase of pulse wave velocity (PWV), and earlier reflections of pulsations, which exaggerates cardiac afterload and coronary perfusion and forms a perfect storm of left ventricular hypertrophy and heart failure[33].

Sympathetic nervous system (SNS) overactivity is a crucial and underestimated cause of endothelial dysfunction and structural remodeling. When hypertension occurs, the SNS is continuously up-regulated with devastating effects way beyond the classical functions of raising the output of the cardiac muscle[34]. Direct harmful effects of chronic adrenergic bombardment at the vascular level occur[35]. The overflow of norepinephrine through perivascular sympathetic nerves stimulates the α_1 -adrenergic receptors on VSMCs, leading to prolonged vasoconstriction and through intracellular signaling pathways such as MAPK, inducing VSMC hypertrophy and proliferation. Moreover, stimulation of the β_1 - β_2 -adrenergic receptors on the juxtaglomerularly located cells of the kidney activates the release of renin, which activates the systemic and local tissue-based renin-angiotensin-aldosterone system (RAAS)[36]. At this point, angiotensin II emerges as a key contributor to the vascular injury to enhance oxidative stress (through Nox activation), inflammation and fibrosis. Endothelial impairment directly results also of sympathetic overactivity; catecholamines may augment endothelial production of ROS and decrease endothelial NO bioavailability[37]. This produces a pathogenic positive feedback mechanism: vascular pathology and heightened rigidity in itself result in dysfunction of the baroreceptors, which further reduces the negative feedback to the central SNS, continuing sympathetic overdrive[38]. Therefore, the SNS is not only a hemodynamic controller but a direct initiator and enhancer of the molecular and cellular events that characterize hypertensive vasculopathy, and therefore, makes the SNS a good therapeutic target. It is the cumulative effects of any treatment, including beta-blockade, which must be evaluated in this composite perspective of neurogenic vascular injury[39].

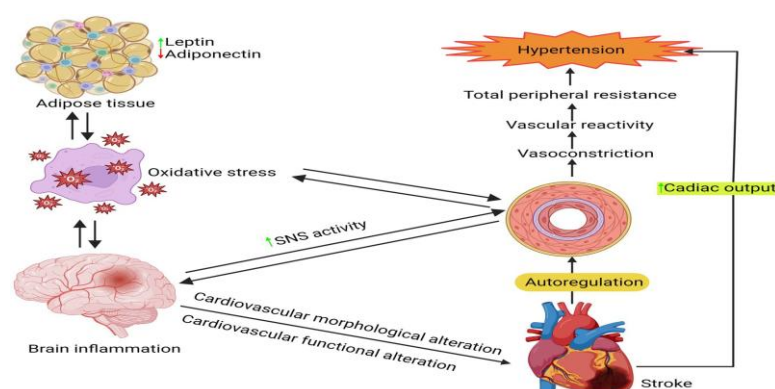


Fig: 2 The Integrated Mechanism of Hypertension-Induced Vascular and End-Organ Damage Pharmacology of Beta-Blockers: A Heterogeneous Class Receptor Selectivity (β_1 , β_2 , β_3)

The heart and kidneys have the highest concentration of β_1 -adrenergic receptors, which dictate the clinical and vascular actions of beta-blockers. β_1 -receptors (e.g., bisoprolol, metoprolol) represent the major antagonists of cardioselective agents, which essentially decelerate the heart rate,

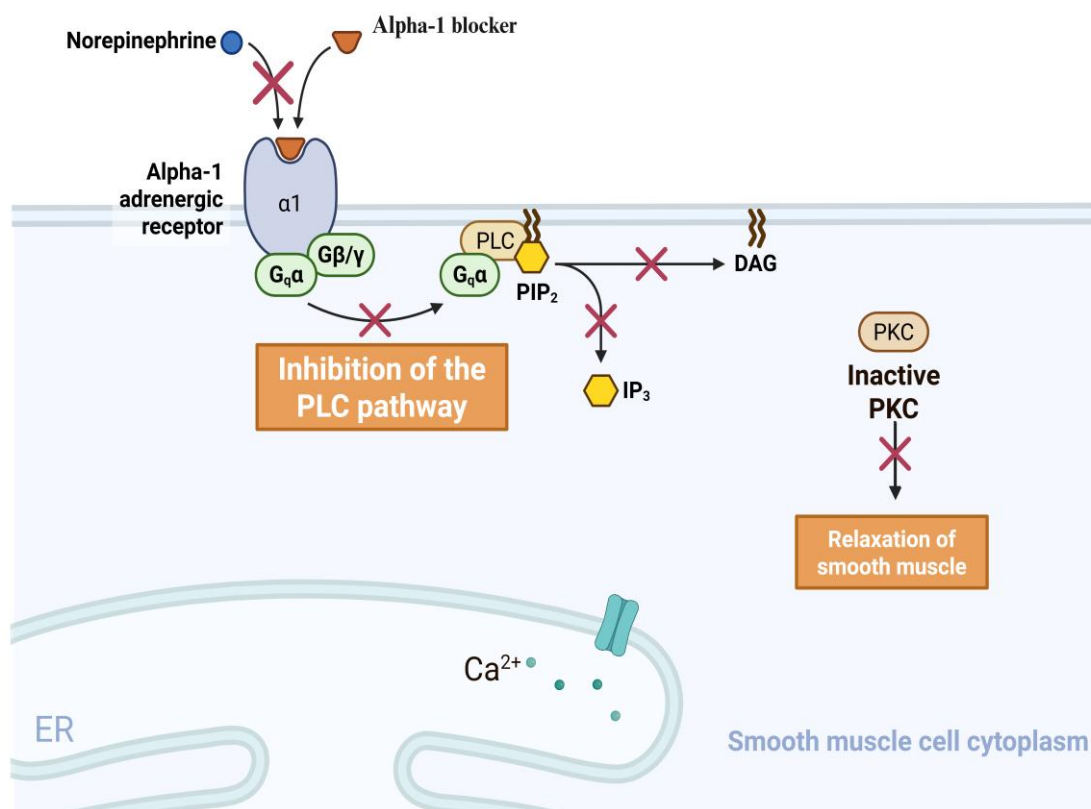
contractility, and renin release[40]. Such selectivity is meant to reduce the direct vascular β_2 -receptor blockage, which is vital because β_2 -mediated signaling generally enhances vascular smooth muscle relaxation does so through cAMP. Non-selective agents (e.g. propranol, nadolol) block both β_1 and β_2 receptors, which may leave α_1 -mediated vasoconstriction unopposed and, at least in the short term, elevate peripheral vascular resistance[41]. The β_3 -adrenergic receptor is a more recently clarified pathway that is mainly found in adipose tissue and endothelium. Its stimulation causes endothelial nitric oxide synthase (eNOS), which causes the opening of the vessels. Nebivol is the only β_1 -selective antagonist that is coupled with β_3 -agonist, whose effect relies on this mechanism, which explains the effect of direct vasodilatory and endothelial-enhancing. Therefore, the selectivity of the receptors is the main determinant of the hemodynamic profile of a beta-blocker and its ability or inability to have direct vascular effect or harm[42][43].

Intrinsic Sympathomimetic Activity (ISA)

The partial agonist behavior of certain beta-blockers (e.g., pindol, acebutol) is known as Intrinsic Sympathomimetic Activity (ISA). In sharp contrast to pure antagonists, such agents have a low degree of intrinsic activity at the β -adrenergic receptor. They stabilize the receptor in a form that activates a submaximal stimulatory response, and at the same time, prevent occupancy of receptor by stronger full agonists such as norepinephrine or epinephrine. This delicate pharmacology produces different hemodynamic and vascular effects. Clinically, the agents that have the ISA property produce less decrease in cardiac output and the resting heart rate than the non-ISA blockers because of the mild stimulatory action that compensates the extreme inhibition. Vas. In theory, ISA, at the β_2 -receptor, could counteract the unopposed α -mediated vasoconstriction of traditional beta-blockade, which may lead to a more neutral acute effect on peripheral vascular resistance[44]. Nevertheless, this partial agonist effect can also compromise the intended cardioprotective and antihypertensive effect at elevations of sympathetic tone as the block is less effective. In turn, although ISA provides an excellent hemodynamic profile in specific environments, its clinical application in the context of hypertension has been restricted by the fear of a reduced effectiveness of the treatment to protect against major cardiovascular events in comparison to other non-ISA agents[45].

Alpha-1 Adrenergic Receptor Blocking Activity

Third-generation vasodilating beta-blockers such as carvedilol and labetalol are characterized by Alpha-1 Adrenergic Receptor Blocking Activity. This dualism is a mixture of non-selective beta-blockade and direct competitive antagonism of postsynaptic α_1 -adrenergic receptors of vascular smooth muscle cells[46]. The vascular implications are far reaching and these agents are different to the traditional beta-blockers. The inhibition of α_1 -receptor fully inhibits the vasoconstriction by norepinephrine via intracellular release of calcium. This actively opposes the possible development of the peripheral vascular resistance that is being induced by the blockage of the beta-2 receptors[47].



Fig; 3 Inhibition of the Alpha-1 Adrenergic Receptor Pathway in Smooth Muscle

The overall effect is the direct arteriolar vasodilation, resulting in the immediate decrease in afterload. It is a key change in the hemodynamic profile of which, whereas pure beta-blockers can decrease blood pressure by lowering the output of the cardiac muscle, carvedilol and labetalol could do it by lowering the output of the cardiac muscle and decreasing systemic vascular resistance[47]. This measure gives it some possible benefits. It causes the development of better acute hemodynamics and possibly better perfusion of the periphery. Moreover, as it avoids the reliance on the reduced cardiac output only, it could limit the compensatory action of other pressor systems. This α_1 -blockade, in turn, is also a contributor to metabolic neutrality (no negative lipid and insulin sensitivity effects of these agents). Their unique pharmacologic characteristics are the basis of their effectiveness in diseases such as heart failure, in which afterload modulation is important, and make them potentially more vasculoprotective in hypertensive patients, especially those with an observed high sympathetic vasoconstrictor tone[48][49].

Additional Properties: Nitric Oxide Potentiation, Antioxidant Effects (e.g., Nebivolol)

In addition to receptor blockade, some of the third-generation beta-blockers have ancillary characteristics, which directly address the vascular dysfunction molecular pathways. The most described is the one which is nitric oxide (NO) potentiation, which is symbolized by nebivol. The effect of nebivol is endothelium-dependent unlike the vasodilation effect of α_1 -blockade. Its active enantiomer, d-nebivol, is a β_3 -adrenergic receptor agonist of the endothelium. β_3 -receptor stimulation triggers phosphatidylinositol 3-kinase (PI3K)/Akt pathway resulting in the phosphorylation of endothelial nitric oxide synthase (eNOS)[50]. This enhances the synthesis of bioactive NO, which facilitates the vasodilation, platelet aggregation, and the growth of vascular smooth muscle cells. This action is an antithesis of endothelial NO deficiency that lies in the heart of hypertensive vasculopathy. Moreover, nebivol and carvedilol have a high level of antioxidant and anti-inflammatory action. Nebivol improves the formation of peroxynitrite, which is a harmful oxidant, by improving NO bioavailability[51]. Carvedilol is a racemic combination with a carbazole ring which provides strong free radical-scavenging properties, regardless of adrenoceptor blocking.

It and its metabolites prevent lipid peroxidation, superoxide anions scavenging and NADPH oxidase. Both of the agents also decrease the expression of adhesion molecules and pro-inflammatory cytokines. These pleiotropic effects, whereby they raise protective NO and reduce destructive oxidative stress, target the underlying redox-inflammatory disequilibrium of the hypertensive vessel wall, and are not just hemodynamic drugs, but would even be vascular repair agents[52].

Generation & Key Trait	Example Drugs	Receptor Selectivity	Vasodilatory Mechanism	Acute Hemodynamic Profile (vs. Pre-Treatment)
First Generation Non-selective	Propranolol, Nadolol, Timolol	β_1 & β_2 antagonist	None. Unopposed α_1 -activity can increase SVR.	↓ Cardiac Index (markedly) ↑ Systemic Vascular Resistance (SVR) Variable effect on PCWP
Second Generation Cardioselective	Atenolol, Metoprolol, Bisoprolol	β_1 antagonist (selective)*	None. Minimal direct vascular effect.	↓ Cardiac Index →/↑ SVR (neutral or mild increase) Variable effect on PCWP
Third Generation Vasodilating	Carvedilol, Nebivolol, Labetalol	Carvedilol: β_1 , β_2 , α_1 antagonist Nebivolol: β_1 antagonist, β_3 agonist	Carvedilol: α_1 -adrenergic blockade & antioxidant effects. Nebivolol: Endothelium-dependent NO release (β_3 -mediated).	Carvedilol: →/↓ Cardiac Index (best preserved) Carvedilol: ↓↓ SVR →/↓ PCWP --- Nebivolol: → Cardiac Index

Clinical Evidence From Bench to Bedside

Vascular function measured directly in humans can give essential data between molecular pharmacology and hard clinical outcome. These studies demonstrate that the degree of division between the classes is very high, and the results greatly depend on the exact beta-blocker agent and the vascular parameter under investigation[53]. FMD is an endothelium-dependent vasodilation of the brachial artery below which is used as a surrogate of systemic NO bioavailability[54]. The heterogeneity of the beta-blocker group is clearly shown in studies based on this gold-standard technique. Neutral or negative effects are always observed with conventional, non-vasodilating beta-blockers such as atenolol and metoprolol. In a pivotal trial reported in the Journal of the American College of Cardiology, although atenolol was effective in reducing blood pressure, it did not enhance and instead deteriorated coronary endothelial dysfunction as an ACE inhibitor. This is in line with many studies of brachial FMD that these agents fail to correct the underlying deficiency of NO, indicating their no direct action on endothelium[56]. The final verdict of any antihypertensive treatment lies on its ability to avert major adverse heart occurrences (MACE). In the case of beta-blockers this body of evidence is seen to have pivotal legacy trials that precipitated a paradigm shift,

meta-analyses that have elicited debate, and new subgroup analyses that suggest a way to personalized application.

Legacy Trials (e.g., MAPHY, ASCOT-BPLA): Lessons on Stroke and Metabolic Outcomes

Early studies that indicated the possibility of cardiovascular benefits of beta-blockade were originally proposed in the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) trial, which compared metoprostrol against thiazide diuretics[54]. Its approach to the method was later questioned. Another conclusive factor to the first-line position of traditional beta-blockers was the Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm (ASCOT-BPLA). This pioneer study involved comparison of atenolol based regimen (containing thiazide) to the amlodipine based regimen (containing ACE inhibitor). In the case of almost equalized brachial systolic blood pressure, the amlodipine based regimen was better in that it recorded a substantial 16-percent decrease in stroke, a 23-percent decrease in cardiovascular mortality and reduced rates of new-onset diabetes. ASCOT-BPLA taught two very important lessons[55]. First, it showed that brachial blood pressure was an inadequate surrogate of vascular protection; the asymmetry in the impact of central aortic pressure with arterial stiffness (as was evident in the CAFE sub-study) was the answer to the stroke discrepancy. Second, it emphasized the negative metabolic effects with the atenolol–thiazide acting in comparison to the calcium channel blocker–ACE inhibitor acting, compromising long-term cardiovascular health. These results solidified the idea that atenolol, and by implication other of its kind were second-line treatment in the case of simple hypertension, and in relation to stroke prevention[56][57].

Meta-Analyses: Interpreting the Heterogeneity

Many meta-analyses attempted to combine the results data of beta-blockers. Major and early studies including the 2007 Lindholm et al. review in *The Lancet* found beta-blockers (mainly atenolol data) to be worse than other classes of drugs in stroke prevention and did not do better in myocardial infarction despite equal blood pressure reduction. Such analyses played a central role in downgrading of guidelines[58]. Nevertheless, one of the most important but continuous shortcomings of most meta-analyses is the fact that all beta-blockers are grouped together as a homogenous group. This method confounds the neutral or adverse effects of atenolol and metoprolol with the perhaps different effects of vasodilating medicines such as nebivolol or carvedilol, of which there are no large-scale, long-term hard-outcome trials in hypertension. Newer meta-analyses which have tried to split out beta-blockers by generation or property imply a more complex image[59][60]. They point out that even though traditional beta-blockers are less effective in terms of stroke risk, their impact on coronary events potentially is closer to other categories, and the risk-benefit of vasodilating beta-blockers seems to be different. The main thing that meta-analyses have taught us is that the conclusion about the presence of the so-called class effect is too simplistic and probably causes the researchers to overlook the potential of pharmacologically advanced agents that have a beneficial effect on the vasculature. The shift to personalised medicine requires the determination of which patient with hypertension is most benefited by beta-blockade[61]. Outcomes of subgroup analysis of trials and pathophysiological arguments indicate that there are some important phenotypes. A typical indication is found in younger or middle-aged patients with a hyperkinetic, high-renin, and high-sympathetic drive type of hypertension (that includes tachycardia, high cardiac output, and anxiety). The initial hemodynamic imbalance in such individuals is cardiac in nature so that decreased heart rate and output become especially effective and physiologically reasonable[62][63]. Clearly identified candidates include patients with certain comorbidities in which beta-blockers have demonstrated outcome benefits in patients with heart failure (reduced ejection fraction), post-myocardial infarction, atrial fibrillation with rapid ventricular response or a history of coronary artery disease. In this case, beta-blockers will cure the hypertension as well as the comorbidity[64][65].

The Special Case of Vasodilating Beta-Blockers (Nebivolol, Carvedilol, Labetalol)

Mechanistic Deep Dive: NO Synergy vs. Alpha-Blockade

The afterload reduction by vasodilating beta-blockers occurs in two different and pharmacologically independent mechanisms, which predetermine the specific vascular characteristics of these agents. Nebivol functions through nitric oxide (NO) synergy through the endothelium[67]. Its active enantiomer is a β_3 -adrenergic receptor agonist which activates a PI3K/Akt-dependent signaling cascade phosphorylating and activating endothelial nitric oxide synthase (eNOS). This enhances endogenous NO production which results in relaxation of the smooth muscle by cGMP. This is essentially an endothelium-dependent, vasoprotective mechanism that directly reverses the NO deficiency of central importance to hypertension. It also has the antioxidant and anti-inflammatory effects since oxidative stress decreases with high levels of NO bioavailability[68].

Conversely, carvedilol and labetalol cause vasodilation with the main mechanism of competition with α_1 -adrenergic receptor blocking[68][69]. It is a direct smooth muscle action that does not depend on the endothelium and antagonizes the effect of norepinephrine on the vasoconstriction. Carvedilol also contributes a major antioxidant dimension that is through its carbazole moiety that scavenges free radicals directly. In such a way, the two approaches decrease peripheral resistance, but nebivol is restorative to endothelial activity, and carvedilol is more inhibitory to constrictor tone and oxidative injury[70]. This mechanistic separation implies there may be discrepancies between their effects of long-term effects on the vascular remodeling and stiffness.

Comparisons with Conventional Beta-Blockers (Atenolol, Metoprolol) on Vascular Parameters

Direct comparative studies provide the consistency of the vascular superiority of vasodilating beta-blockers compared to conventional ones[71]. Nebivolol and carvedilol invariably enhance the endothelial activity in flow-mediated dilation (FMD) studies, but atenolol and metoprolol demonstrate neutral or deteriorating effects. Indicatively, a Hypertension randomized trial indicated that nebivol was much better than metoprolol in enhancing FMD though both drugs had an equivalent decrease in brachial blood pressure[72].

In terms of arterial stiffness, which was quantified by pulse wave velocity (PWV), the difference is as well as dramatic[73]. Atenol normally exerts little influence on PWV and that is why it does not decrease central aortic pressure effectively in such a trial as ASCOT-CAFE. On a head to head comparison, both nebivol and carvedilol have been found to decrease PWV significantly compared to atenolol[74][75]. Research has also indicated that vasodilating agents result in a greater decrease in central systolic pressure and augmentation index (a parameter which measures wave reflections) in comparison to their traditional counterparts. This evidence supports the validation of the claim that the negative vascular events associated with beta-blockers are not a class effect but occur specifically in agents that do not have either direct vasodilatory or endothelial-enhancing activity[76].

Clinical Outcomes and Applications

Although they are not supported by large, hard-outcome trials of vasodilating beta-blockers in simple hypertension, their good metabolic and hemodynamic effects establish certain niches. Nebivol and carvedilol are metabolically neutral in patients with hypertension and metabolic syndrome or insulin resistance as opposed to traditional beta-blockers that aggravate insulin sensitivity and lipid profiles. This makes them superior in this case when a beta-blocker is being prescribed in this increasing number of patients[78][79]. One promising and biologically plausible niche is heart failure with preserved ejection fraction (HFpEF) condition closely associated with hypertension, endothelial dysfunction, and ventricular-vascular stiffening. The exclusive property of nebivol (NO-mediated) and carvedilol (antioxidant, anti-fibrotic) to potentially enhance ventricular compliance and coronary microvascular function is being studied[80]. Although they have not yet become a guideline-recommended indication, their mechanism is more consistent with the pathophysiology than traditional beta-blockers. In addition to this, a vasodilating beta-blocker can

provide the required heart rate control in patients with hypertension and some sympathetic overdrive (e.g., tachycardia, anxiety) in the presence of peripheral vascular disease or Raynaud phenomenon, [81][82] which is one of the major pitfalls of traditional treatment[84][85]. These applications highlight the concept of to tailor the drug to the patient by aligning its particular pharmacodynamic profile with the predominant pathophysiology in the patient[85].

Conclusion

The changing role of beta-blockers in hypertension highlights a new shift towards a vascular-based approach of treatment as opposed to a hemodynamic approach. The downgrading of this drug group in major guidelines, which in large part rests upon evidence of more traditional agents such as atenolol, is a commendable focus on the therapies that directly reverse endothelial dysfunction, remodeling, and arterial stiffness the pathophysiological events underlying cardiovascular risk. Nevertheless, a single classification of beta-blockers is both scientifically and clinically outdated. There is an overall pharmacological heterogeneity in the class. Traditional, non-vasodilating beta-blockers reduce blood pressure only by reducing cardiac output, and tends to have neutral or deleterious direct action on the vasculature and metabolism. Contrastingly, third generation vasodilating beta-blockers (nebivol, carvedilol, labetalol) also have ancillary properties, including nitric oxide potentiation, α_1 -adrenergic blockade and anti-oxidant properties, which actively enhance endothelial activity, decrease arterial rigidity and is metabolically neutral. Therefore, the use of beta-blockers in the treatment of hypertension should be more subtle and individualistic. A rational and vasculoprotective option to use against particular types of hypertension is considered the vasodilating beta-blockers; they should be considered in patients with high sympathetic drive, in metabolic syndrome, as a component of a bespoke combination therapy, or when used concomitantly with heart failure or atrial fibrillation. Future recommendations and clinical practice must go beyond a general rule and consider various subtypes of beta-blockers and match the unique pharmacologic characteristics of each agent with the predominating pathophysiology of the patient being treated. It is not blood pressure reduction to the final end but vascular restoration, and such can be achieved with the contemporary beta-blocker pharmacopeia wisely applied.

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