Pharmacological Augmentation of Endothelium-Derived Nitric Oxide Synthesis

George L. Bakris, MD, FACP, FAHA, FASN

ABSTRACT

BACKGROUND: The sympathetic nervous system has a unique role in endothelial function, and beta-receptors are a key part of sympathetic nervous system function.

OBJECTIVE: To elucidate the pharmacological augmentation of endothelium-derived nitric oxide synthesis.

SUMMARY: Beta-blockers have been commercially available since the 1960s. Stimulating beta-receptors causes dilatation whereas blocking beta-receptors, as traditional beta-blockers do, cause vasoconstriction. However, beta-blockers are hypotensives. This effect probably occurs because they inhibit renin in the kidney and juxtaglomerular apparatus, especially at high doses. They also have some central effects because of central inhibition of the sympathetic nervous system that also lowers blood pressure. In addition, evidence suggests that beta-blockers work at the vascular biology level to produce nitric oxide release. Beta-blockers differ in terms of their beta-receptor selectivity, intrinsic sympathomimetic activity, and benefit/risk in diabetes and insulin sensitivity.

Nebivolol, the newest of the beta-blockers, is long acting and the most cardioselective beta₁-blocker currently available. Nebivolol-induced endothelium-dependent vasodilation associated with activation of the L-arginine/nitric oxide pathway may confer benefits to patients. The risk for diabetes is lower, the metabolic effects are lower, and people with diabetes who have clear nitric oxide dysfunction may have particular benefits from this agent.

CONCLUSION: Third-generation beta-blockers, such as labetalol, carvedilol, bucindolol, and nebivolol, vasodilate by different mechanisms, behaving differently than traditional beta blockers and offering different benefits.

KEYWORDS: Beta-adrenergic receptors, Beta-blockers, Nebivolol, Third-generation beta-blockers, Hypertension, Nitric oxide

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A panoply of vascular issues forms the cardiovascular continuum and suggests new targets for drug therapy (see figure). As with any chronic condition, primary prevention is the best and most important step. Any intervention or lifestyle change should target things that lead to endothelial dysfunction, one of the earliest manifestations of vascular inflammation. "Appropriate interventions to prevent vascular inflammation include smoking cessation, regular exercise, weight loss, and reduction of dietary fat consumption."¹

One sign of endothelial dysfunction is the presence of microalbuminuria. Microalbuminuria is an early red flag that a problem with the vasculature is present. The kidney, as the most vascular organ in the body, will allow small amounts of albumin in the urine, indicative of subclinical cardiovascular disease, that cannot

FIGURE

Central Role of Intermediate Endpoints in the CV Continuum and New Targets of Therapy

Volpe M, Tocci G, Pagannone E. *J Am Soc Nephrol.* 2006.

AF=atrial fibrillation; AMI=acute myocardial infarction; BP=blood pressure; CHF=congestive heart failure; ESRD=end-stage renal disease; IGT=impaired glucose tolerance; LVD=left ventricular dysfunction; LVH=left ventricular hypertrophy.

Author

GEORGE L. BAKRIS, MD, FACP, FAHA, FASN, is a professor of medicine and director, Hypertension Unit, Section of Endocrinology, Diabetes, and Metabolism, University of Chicago-Pritzker School of Medicine, Illinois.

AUTHOR CORRESPONDENCE: George L. Bakris, MD, Director, University of Chicago, Section of Endocrinology, Diabetes, and Metabolism, 5841 S. Maryland Ave., MC1027, Chicago, IL 60637. Tel: (773) 702-7936; Fax: (773) 834-0486; E-mail: gbakris@earthlink.net

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be detected by urine dipstick methods. Vascular endothelial dysfunction indicates that atherosclerotic processes are under way and hypertension is beginning. The risk for new-onset diabetes increases substantially. Kidney function eventually becomes impaired because the kidney cannot regulate the higher pressure. Ultimately over many years, myocardial infarction (MI), kidney failure, or heart failure may develop.

The sympathetic nervous system has a unique role in endothelial function, and beta-receptors are a key part of sympathetic

nervous system function. As hormones are released, they interact with the following beta-receptors:

- Beta₁-receptors predominate in healthy cardiac muscle over beta₂-receptors.
- Beta₂-receptors predominate in the lungs.
- Alpha₁-receptors mediate endothelial function and vasoconstriction in peripheral vessels, regulate blood flow to the kidneys, and have been implicated in myocardial hypertrophy and benign prostatic hyperplasia.
- Stimulating beta-receptors causes dilatation.²

Beta-blocker mechanisms are interesting. Beta-blockers should cause hypertension via beta-receptor blockade, and traditional beta-blockers do vasoconstrict. However, beta-blockers are hypotensives. This effect probably occurs because beta-blockers inhibit rennin in the kidney and juxtaglomerular apparatus, especially at high doses. They also have some central effects because of central inhibition of the sympathetic nervous system (i.e., baroreceptor effects) that also lower pressure. Their ability to slow the heart rate also contributes to lower blood pressure (BP).

Beta-blockers have been commercially available since the 1960s. At this time, the third-generation beta-blockers include labetalol (a nonselective drug with higher affinity for the alpha₁-receptor than for beta₁- and beta₂-adrenergic receptors); carvedilol (beta₁ selective drug that becomes less selective at higher doses and provides alpha₁-receptor blockade); bucindolol (nonselective drug that inhibits the alpha₁-receptor); and nebivolol (higher beta₁ selectivity than other beta-blockers, with endothelium-dependent vasodilation associated with activation of the L-arginine/nitric oxide [NO] pathway). These beta-blockers vasodilate by different mechanisms, behaving differently than traditional beta-blockers and offering different benefits.

Although beta-blocker subclasses do not appear to differ significantly in antihypertensive efficacy, beta₁-selective agents may be more effective than nonselective beta-blockers. Beta-blockers with intrinsic sympathomimetic activity have been shown to have fewer clinical benefits in post-MI patients and precipitate heart failure in high-risk patients.² This reduces their clinical utility. Beta-blockers differ in terms of benefit/risk in diabetes and insulin sensitivity. The third-generation beta-blocker carvedilol improves insulin sensitivity while older beta-blockers—propranolol, atenolol, and metoprolol—are associated with decreased insulin sensitivity.

Additionally, endothelial-active antihypertensive agents are now available and inhibit free radical production and prevent activation of adhesion molecules. They also prevent platelet aggregation and inactivation of endogenous tissue plasminogen activator. Preventing these atherosclerosis-forming mechanisms can reduce the burden of disease.³

The Newest: Nebivolol

Nebivolol is the newest of the beta-blockers. Nebivolol is a long-acting, highly cardioselective beta-blocker. It is the most selective beta₁-blocker currently available. Its beta₁ selectivity exceeds that

of bucindolol, propranolol, and carvedilol (which have beta₁/beta₂ ratios of about 5); of metoprolol (which has a beta₁/beta₂ ratio of about 80); and of bisoprolol (which has a beta₁/beta₂ ratio of about 125). Its dual mechanism of action includes (1) selective beta₁-receptor blockade and (2) stimulation of endothelial NO production. These 2 mechanisms work in concert on BP. Its pharmacokinetic profile is appropriate for once-daily dosing.⁴

NO mediates stimulation of endothelium-dependent vasodilation. To determine if nebivolol possesses NO-mediated vasodilation effects in man, researchers (Bowman et al.) infused nebivolol alone, and then with a NO inhibitor. This allowed them to determine if NO-mediated mechanisms were at work. Given alone, nebivolol produced dose-dependent venodilation, but when administered with L-NMMA (NG-monomethyl-L-arginine, an NO inhibitor), venodilation was reduced markedly. NO is thus an important part of nebivolol's vasodilating ability.⁵

Nebivolol's potential value rests in its dose-dependent BP reduction that appears to peak at 5 to 10 milligrams. These doses can be expected to result in reductions of 10 to 12 millimeters of mercury.⁶ A double-blind randomized multicenter study by Grassi et al. compared nebivolol's efficacy and tolerability to that of atenolol over 12 weeks. Middle-aged people with mild-to-moderate essential hypertension were randomized to nebivolol 5 mg daily (n=105) or atenolol 100 mg daily (n=100) after a placebo run-in phase.

Nebivolol and atenolol had similar and significant antihypertensive effects. Nebivolol's effect on sitting BP at 12 weeks was slightly better than atenolol's. Both reduced sitting and standing heart rates significantly, but nebivolol caused less bradycardia than did atenolol. Study subjects were better able to tolerate nebivolol and reported fewer side effects.⁷

Again, comparing nebivolol and atenolol (in the Grassi study), researchers have confirmed that nebivolol and atenolol reduce SBP and DBP similarly, and that atenolol-treated study subjects tend to have significantly lower heart rates. But researchers found a significant difference in stroke volume. After 2 weeks of treatment with nebivolol, mean stroke volume increased significantly and heart rate slowed significantly, leading to a slight increase in cardiac output that was nonsignificant. Peripheral resistance was reduced significantly.

After 2 weeks of treatment with atenolol, mean stroke volume increased slightly (this was not significant) and heart rate slowed. Cardiac output was reduced and peripheral resistance increased, again in a nonsignificant manner. Atenolol's antihypertensive effect was attributed to cardiac output and heart rate reduction. Nebivolol's antihypertensive effect was attributed to reduced peripheral resistance and increased stroke volume with preserved cardiac output. Both drugs reduce heart rate, which is a benefit.

In terms of end diastolic volume, nebivolol creates almost double the benefit of that seen with atenolol (a change of 10.6% vs. 5.7%, respectively). Nebivolol may be even more beneficial than atenolol to prevent heart failure due to its better end systolic volume (a change of 9.2% vs. -0.49%, respectively).⁸

Using a small mouse model, Georgescu et al. investigated the cellular mechanisms by which nebivolol induces renal artery vasodilation.⁹ They found that the cellular mechanisms of nebivolol's vasodilator effect on the renal artery include activation of the endothelial β_2 -adrenoceptor, participation of calcium-activated potassium channels, and an increase in NO and NO synthase. Nebivolol's profound vasodilating ability was dose dependent. NO blockade stopped vasodilation almost totally.

A separate study by Kalinowski et al. looked at renal arteries in rats, attempting to determine how nebivolol stimulates NO release from microvascular endothelial cells.¹⁰ The researchers found that nebivolol induces relaxation of renal glomerular microvasculature, using adenosine triphosphate efflux with consequent stimulation of P2Y-purinoceptor-mediated NO release from glomerular endothelial cells. The magnitude of the endothelial NO stimulation and release in the kidney was indisputable.

Chronic inhibition of NO synthesis can lead to arterial hypertension. In another rat study by Fortepiani et al., researchers administered nebivolol (1 mg/kg/day, 14 days) concurrently with the NO synthesis inhibitor NW-nitro-L-arginine methyl ester (L-NAME, 0.1, 1, and 10 mg/kg/day, 14 days).¹¹ Although glomerular filtration rate and natriuresis remained similar in nebivolol-treated and -untreated rats, nebivolol completely prevented arterial hypertension in the L-NAME 0.1 and 1 mg/kg/day groups. It reduced the BP increase expected in the L-NAME 10 mg/kg/day dose. Nebivolol's ability to prevent arterial hypertension associated with chronic NO deficit appears to be related to inhibition of the renin-angiotensin system.

The traditional beta-blockers worsen glucose and lipid parameters in diabetics.¹²⁻¹⁷ Might nebivolol be a more acceptable and effective antihypertensive in people who have concomitant aberrations of lipid metabolism or diabetes? In an observational study (N=6,376) comparing adult patients with arterial hypertension with and without comorbid conditions (including diabetes), patients were treated with 5 mg nebivolol daily, with older adults (older than 65 years) receiving 2.5 mg. At the end of 6 weeks, significant decreases in SBP and DBP were observed, with 62.2% of the patients reaching normal BPs. Heart rate also improved. During the study, triglycerides fell 13% and cholesterol fell 8%. In diabetic patients, those results were more pronounced (triglycerides decreased 18% and cholesterol 9%). Glucose decreased in diabetics by 16%.¹⁸ Nebivolol monotherapy improves glucose and lipid parameters, even in patients with diabetes.

Summary

Third-generation beta-blockers do provide better tolerability than do traditional agents and may have added benefits due to vasodilating properties. The term "class effect" may now be obsolete for beta-blockers. Older agents (propranolol, atenolol, etc.) were similar with subtle differences in cardio-selectivity, but evidence indicates that effects unrelated to adrenergic blockade are working at the vascular biology level to produce NO release. The newest of

the third-generation beta-blockers, nebivolol, offers higher β_1 selectivity, the highest available compared with other beta-blockers. Endothelium-dependent vasodilation associated with activation of the L-arginine/NO pathway may confer benefits on the patients. The risk for diabetes is lower, the metabolic effects are lower, and people with diabetes who have clear NO dysfunction may have particular benefits from this agent.

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