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The Role of Vasodilating β-Blockers in Patients with Hypertension and the Cardiometabolic Syndrome

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ABSTRACT

In the United States, a vast segment of the adult population is classified as having the cardiometabolic syndrome, and currently there are epidemic rates of both type 2 diabetes mellitus and obesity. Hypertension is closely linked with these metabolic disorders and is a strong independent predictor of incident type 2 diabetes. In addition, hypertension is an important contributor to increasing cardiovascular disease risk in patients with the cardiometabolic syndrome. Lowering elevated blood pressure in patients with the cardiometabolic syndrome or diabetes is a critical component of reducing global cardiovascular risk. However, aggressive management of hypertension in these patients is often challenging, and the presence of these conditions is associated with poor blood pressure control. The utility of β-blockers in patients with these conditions continues to be a subject of intense debate, given the adverse metabolic effects associated with conventional β-blockers. Data on vasodilating β-blockers, however, suggest that these agents have favorable or neutral metabolic effects and generally more favorable effects when compared with nonvasodilating members of this class. These agents may expand the utility of β-blockers to patient populations traditionally considered not to be optimal candidates for β-blocker therapy—a fact which has important clinical implications, because more antihypertensive agents are needed to diversify the therapeutic options available for clinicians treating hypertension in patients with the cardiometabolic syndrome or type 2 diabetes.

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KEYWORDS: β-Blockers; Diabetes mellitus; Hypertension; Cardiometabolic syndrome; Nebivolol; Vasodilating β-blockers

A vast segment of the adult population in the United States—between 35% and 39%, depending on the criteria used in the National Health and Nutrition Examination Survey (NHANES)—has cardiometabolic syndrome.[1] The United States also currently faces epidemics of both type 2 diabetes mellitus and obesity.[2] Because the prevalence of the cardiometabolic syndrome and diabetes increases with age,[3] it is expected that even greater numbers of adults in the United States will be affected with these diseases as the overall population ages in the coming decades.

Hypertension is closely linked with the cardiometabolic syndrome and diabetes, with blood pressure and blood pressure progression being strong and independent predictors of incident type 2 diabetes.[4] In the Atherosclerosis Risk in Communities (ARIC) study, type 2 diabetes was almost twice as likely to develop in subjects with hypertension than in their normotensive counterparts.[5] High blood pressure—along with abdominal obesity, low high-density lipoprotein (HDL) cholesterol levels, high levels of triglycerides, and insulin resistance/elevated glucose—is a key component of the cardiometabolic syndrome.[6] Moreover, hypertension is a particularly important contributor to increasing cardiovascular disease (CVD) risk in patients with this syndrome. In the ARIC study, not only did hypertension (along with hypertriglyceridemia) serve as the strongest independent risk factor for atherosclerosis progression, it also contributed the most to amplifying CVD risk in the setting of other cardiometabolic syndrome risk factors.[7]

As a consequence, lowering elevated blood pressure in patients with the cardiometabolic syndrome or diabetes is a

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vital consideration in reducing global cardiovascular risk. In the United Kingdom Prospective Diabetes Study Group (UKPDS), tight blood pressure control (defined as <150/85 mm Hg) significantly reduced diabetes-related macrovascular events, compared with less-rigorous control (defined as <180/105 mm Hg).[8] In particular, the group assigned to tight blood pressure control had a significant 44% reduction in fatal and nonfatal stroke, as well as a nonsignificant 21% reduction in myocardial infarction.[8] Recent follow-up data from UKPDS, however, indicate that aggressive blood pressure control must be sustained over the long term to maintain this cardiovascular benefit.[9]

Aggressive management of hypertension in patients with the cardiometabolic syndrome or diabetes is challenging for multiple reasons, and the presence of these diseases is associated with poor blood pressure control.[10] In the Global Cardiometabolic Risk Profile in Patients with hypertension disease survey study (N = 3,370), <33% of treated patients with hypertension had controlled blood pressure.[10] One reason for blood pressure control being challenging in these circumstances is the need to use multiple medications, either because of the accentuated elevation in blood pressure or particular comorbidities that preclude the use of certain medications or increase the risk of side effects with particular drugs. In UKPDS, on average, ≥3 drugs were needed to achieve tight blood pressure control.[8] Exacerbations of metabolic aspects of diabetes or the metabolic syndrome are a reasonable concern with some antihypertensive agents. The side effects of coadministered drugs are potentially greater than the sum of the parts might simply predict. Thus, the selection of drugs for initial and continuing long-term combination treatment is an important clinical consideration for these patient populations.[11]

METABOLIC EFFECTS OF CONVENTIONAL β-BLOCKERS

Despite the recommendations for β-blocker use in patients with hypertension at high risk for CVD, including patients with diabetes, in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7),[12] the utility of β-blockers in patients with the cardiometabolic syndrome or type 2 diabetes was debated vigorously.[11,13] Abnormalities of glucose, insulin, and lipid and carbohydrate metabolism have been reported frequently during treatment with conventional β-blockers, particularly in pooled data sets.[14-19] A meta-analysis of >400 clinical trials reported between 1966 and 1993 showed that conventional β-blockers were associated with an increase in plasma triglyceride levels and an associated decrease in HDL cholesterol levels.[16] Overall, antihypertensive treatment with agents such as metoprolol, atenolol, propranolol, and pindolol decreases insulin sensitivity.[18] In a study of metoprolol succinate in patients with essential hypertension using the hyperinsulinemic euglycemic glucose clamp technique (the "gold standard" for measuring insulin sensitivity[18]), the insulin sensitivity index decreased by 22% ($P = 0.0025$) during treatment.[14]

Although many patients with hypertension develop diabetes even when treated with placebo, it also is well recognized that conventional β-blockers can cause clinically significant elevations in glucose concentrations[20] and increase the risk of new-onset diabetes.[5,21,22] In the ARIC study, patients with hypertension taking β-blockers had a 28% increased risk of developing diabetes compared with subjects with hypertension who did not take any medication ($P < 0.05$), even after controlling for family history of diabetes, as well as demographic and clinical characteristics such as age, race, adiposity, physical activity level, and coexisting illnesses.[5] In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, an analysis of 7,998 patients without diabetes at baseline showed that treatment with atenolol was associated with a 25% increased risk of new-onset diabetes compared with losartan treatment ($P < 0.001$).[21]

Two meta-analyses have provided additional support for these findings.[23,24] In a recent, thorough, and comprehensive network meta-analysis of 22 clinical trials mostly in patients with hypertension, Elliott and Meyer[23] documented the odds ratio (OR) of new-onset diabetes compared with placebo to be highest with diuretics (OR, 1.30; 95% confidence interval [CI], 1.07-1.58; $P = 0.009$) and β-blockers (included studies using predominantly atenolol or metoprolol) (OR, 1.17; 95% CI, 0.98-1.40; $P = 0.08$) and lowest with angiotensin II receptor blockers (ARBs) (OR, 0.75, 95% CI, 0.61-0.91; $P = 0.003$) and angiotensin-converting enzyme (ACE) inhibitors (OR, 0.87; 95% CI, 0.75-1.01; $P = 0.064$). A meta-analysis by Bangalore and colleagues[24] evaluated randomized controlled trials of patients taking β-blockers as first-line therapy for hypertension and included 12 studies involving 94,492 patients. Their findings showed that β-blocker therapy was associated with a 22% increased risk for new-onset diabetes (relative risk, 1.22; 95% CI, 1.12-1.33) compared with nondiuretic antihypertensive agents.[24]

Some authors have estimated that β-blockers and diuretics could account for >100,000 cases of new-onset diabetes in the United States every year.[11] In fact, the less-than-expected reductions in CVD outcomes seen in many trials of conventional β-blockers frequently have been attributed to the potentially adverse metabolic effects of these agents.[11] Recent results of large randomized clinical trials in hypertension, such as LIFE[21] and the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA),[22] have demonstrated higher CVD mortality with atenolol-based treatment compared with other classes of drugs. Because there is a direct continuous association between HbA_{1c} and CVD risk, the potential negative consequences of even small increases in glucose are considerable.[25]

AGGRESSIVE MANAGEMENT OF HYPERTENSION IN PATIENTS WITH THE CARDIOMETABOLIC SYNDROME: THE ROLE OF VASODILATING β-BLOCKERS

The β-blockers included in the meta-analyses and other reports in the literature predominantly are older, conventional agents of this class. β-Blockers comprise a highly heterogeneous class of agents, however, with a range of pharmacologic, hemodynamic, and metabolic effects. In the meta-analysis reported by Kasiske and colleagues,[16] for example, the increase in triglycerides seen with β-blockers overall was smaller with cardioselective β-blockers and those with intrinsic sympathomimetic activity (ISA), and agents with both cardioselectivity and ISA reduced both total and low-density lipoprotein cholesterol levels.

Clinical trial data suggest that vasodilating β-blockers, such as carvedilol, a β_1/β_2-antagonist with α_1-blocking activity,[26] and nebivolol, a highly β_1-selective agent with nitric oxide (NO)–mediated vasodilatory effects,[26-28] have neutral or even beneficial metabolic effects, and thus can be potentially useful in patients with hypertension who have or are at risk for the cardiometabolic syndrome or diabetes. The Glycemic Effects in Diabetes Mellitus: Carvedilol–Metoprolol Comparison in Hypertensives (GEMINI) trial[19] compared carvedilol with the nonvasodilating agent metoprolol in 1,235 patients with hypertension and type 2 diabetes. All patients received background therapy with a renin-angiotensin system (RAS) blocker. Results showed that the addition of carvedilol, compared with metoprolol, had a favorable effect on glycemic control, insulin resistance, microalbuminuria, and body weight.[19] For example, there was a 9% reduction in insulin resistance (as measured by the homeostasis model of assessment [HOMA]) when carvedilol was added to existing therapy, leading to a 7% difference between the carvedilol and metoprolol groups.[19] That the differences between metoprolol and carvedilol were observed in the presence of an ACE inhibitor or an ARB—agents known to have favorable effects on metabolic parameters—is important, as it suggests that the metabolic effects of β-blockers remain clinically significant even in the context of metabolically salutary RAS blockade.[13] Thus, combination antihypertensive therapy, even with RAS agents, has the potential to cause further favorable, or less favorable, metabolic responses. RAS-blocking agents are reasonable therapies with which to evaluate coadministration data, because they are likely to be given as a part of multidrug therapy in patients with diabetes, impaired glucose tolerance, or the cardiometabolic syndrome.

The highly β_1-selective agent nebivolol has vasodilatory properties that are mediated by its stimulation of NO release from endothelial cells.[29,30] Based on the hemodynamic theory of insulin resistance, the vasodilatory mechanism attributed to nebivolol may have important implications for its metabolic effects.[17] This theory is based on the finding that improvement in arterial perfusion (i.e., paucity of vasoconstriction) of skeletal muscle improves insulin sensitivity, and that insulin-mediated glucose uptake in muscle is closely linked to endothelium-dependent vasodilation.[31] Two studies comparing nebivolol with atenolol, one in patients with hypertension and impaired glucose tolerance and elevated body mass index (BMI)[32] and the other in patients with hypertension and type 2 diabetes,[33] showed neutral effects of nebivolol on insulin sensitivity; the former also showed a deleterious effect of atenolol (20% reduction in insulin sensitivity).[32] In another small (n = 10) crossover study of patients with hypertension and type 2 diabetes, treatment with nebivolol 5 mg once daily resulted in a small increase in total body insulin sensitivity ($+0.02 \pm 1.16$ mL/min/m^2/μU/mL), whereas enalapril 10 mg once daily resulted in a small decrease (-0.23 ± 0.73 mL/min/m^2/μU/mL). Although the study did not demonstrate a statistically significant difference in the levels of total body insulin sensitivity associated with each agent, and although there were no significant differences between treatments in blood vessel insulin sensitivity, it did indicate an absence of the problematic worsening of insulin sensitivity often ascribed to β-blocker therapy.[34] Nebivolol demonstrated insulin sensitivity characteristics similar to, and in the cited instance a bit numerically better than, an ACE inhibitor. Small sample sizes and other design issues, such as a relatively low dosage of atenolol (50 mg/day) in the study in patients with hypertension and type 2 diabetes,[32] may limit interpretation of the results of these studies.[35]

A larger, double-blind, randomized clinical study comparing nebivolol 5 mg once daily with metoprolol 100 mg once daily for 6 months was conducted with newly diagnosed patients with hypertension who had no evidence of insulin resistance at baseline and a normal BMI.[17] Results showed that nebivolol significantly reduced HOMA insulin resistance ($P = 0.008$), whereas metoprolol slightly increased HOMA insulin resistance (P = NS); the difference between treatments was statistically significant ($P = 0.003$) (Figure 1).[17] The metabolic effects of nebivolol have also been assessed in the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS), a large, placebo-controlled, double-blind, randomized outcome trial in elderly patients.[36] A recently published analysis of metabolic data from this trial reported that fasting serum glucose levels decreased in the subgroup of patients with diabetes at baseline, by −0.32 mmol/L in the nebivolol group and by −0.11 mmol/L in the placebo group, whereas there were no changes with either treatment in patients without diabetes at baseline (0.03 mmol/L and 0.05 mmol/L, respectively).[37] Of note, there were fewer cases of new-onset diabetes in the nebivolol group than in the placebo group, although the difference did not reach statistical significance (Figure 2).[37] Finally, 2 large placebo-controlled phase 3 studies of patients with hypertension treated with nebivolol, either alone (n = 909) or as an add-on to other antihypertensive agents (n = 669), in which 10% to 14% of patients had diabetes at baseline, showed no changes in blood glucose during 12 weeks of therapy with either nebivolol or placebo.[38] Long-

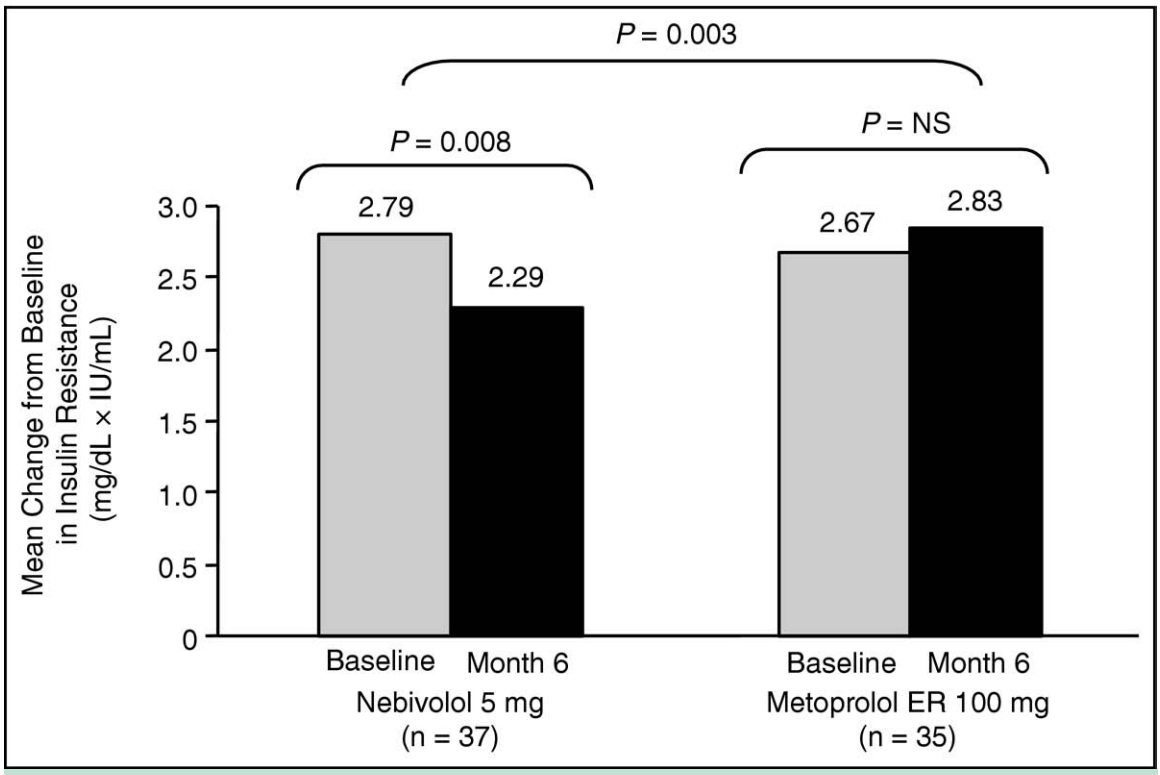

Figure 1 Comparative effects of nebivolol and metoprolol on insulin resistance. (Adapted from *J Hypertens*.[17])

term nebivolol treatment, assessed during a 9-month open-label extension study in patients with hypertension, also showed persistently neutral glycemic effects, with no observed changes in blood glucose at follow-up.[39] To date, no head-to-head studies have been conducted to compare the metabolic effects of nebivolol with carvedilol or labetalol.

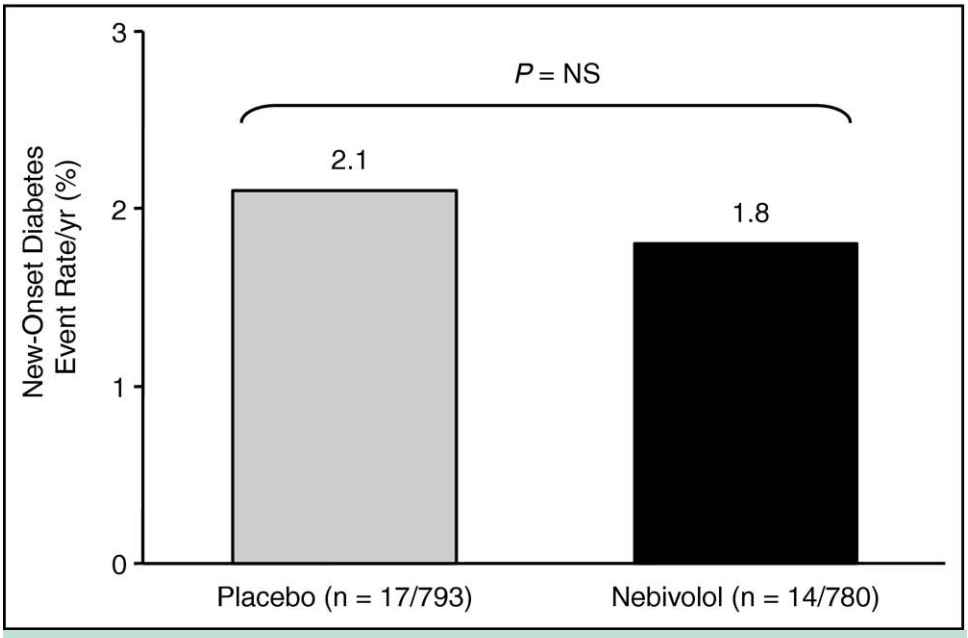

Figure 2 Development of new-onset diabetes with placebo and nebivolol in the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS). (Adapted from *Drugs*.[37])

SUMMARY

Clearly, more agents are needed to diversify the antihypertensive armamentarium and to provide more choices for clinicians in achieving the recommended aggressive blood pressure control for patients with the cardiometabolic syndrome or type 2 diabetes. To this end, data on vasodilating β-blockers, such as nebivolol, carvedilol, and labetalol, suggest that these agents have favorable or neutral metabolic effects, and generally more favorable effects, when compared with older, nonvasodilating members of this class. Recognizing the key role of combination therapy, vasodilating β-blockers have also been shown to maintain favorable or neutral metabolic effects in patients with hypertension, including those with coexisting diabetes, when used in combination with other antihypertensive drugs, including RAS-blocking agents.

AUTHOR DISCLOSURES

The authors who contributed to this article have disclosed the following industry relationships:

Addison A. Taylor, MD, PhD, is a member of the Speakers' Bureaus of Abbott Laboratories, Boehringer Ingelheim, Forest Laboratories, Inc., GlaxoSmithKline, Merck & Co., Inc., and Novartis AG; has worked as a consultant to Abbott Laboratories, Boehringer Ingelheim, Forest Laboratories, Inc., GlaxoSmithKline, Merck & Co., Inc., and Novartis AG; has served on the advisory boards of Abbott Laboratories, Boehringer Ingelheim, Forest Laboratories, Inc., GlaxoSmithKline, Merck & Co., Inc., and Novartis AG; and has received research/grant support from Abbott Laboratories, Bristol-Myers Squibb Company, Forest Research Institute, Inc. (a subsidiary of Forest Laboratories, Inc.), Merck & Co., Inc., Novartis AG, Pfizer Inc, and sanofi-aventis.

George L. Bakris, MD, has worked as a consultant to Abbott Laboratories, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Boehringer Ingelheim, CVRx, Inc., Forest Laboratories, Inc., Gilead Sciences, Inc., GlaxoSmithKline, Merck & Co., Inc., Novartis AG, Takeda Pharmaceuticals North America, Inc., and Walgreen Co.; and has received research/grant support from CVRx, Inc., Forest Laboratories, Inc., and GlaxoSmithKline.

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