Beta-Blockers in Hypertension

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Beta blockers have been used in the treatment of cardiovascular conditions for decades. Despite a long history and status as a guideline-recommended treatment option for hypertension, recent meta-analyses have brought into question whether β blockers are still an appropriate therapy given outcomes data from other antihypertensive drug classes. However, β blockers are a heterogenous class of agents with diverse pharmacologic and physiologic properties. Much of the unfavorable data revealed in the recent meta-analyses were gleaned from studies involving nonvasodilating, traditional β blockers, such as atenolol. However, findings with traditional β blockers may not be extrapolated to other members of the class, particularly those agents with vasodilatory activity. Vasodilatory β blockers (i.e., carvedilol and nebivolol) reduce blood pressure in large part through reducing systemic vascular resistance rather than by decreasing cardiac output, as is observed with traditional β blockers. Vasodilating ability may also ameliorate some of the concerns associated with traditional β blockade, such as the adverse effects on metabolic and lipid parameters, including an increased risk for new-onset diabetes. Furthermore, vasodilating ability is physiologically relevant and important in treating a condition with common co-morbidities involving metabolic and lipid abnormalities such as hypertension. In patients with hypertension and diabetes or coronary artery disease, vasodilating β blockers provide effective blood pressure control with neutral or beneficial effects on important parameters for the co-morbid disease. In conclusion, it is time for a reexamination of the clinical evidence for the use of β blockers in hypertension, recognizing that there are patients for whom β blockers, particularly those with vasodilatory actions, are an appropriate treatment option. **(Am J Cardiol 2010;106:1819–1825)**

Building on the availability of propranolol since 1976, more than a dozen additional β blockers have been introduced for hypertension treatment.[1,2] This antihypertensive drug class effectively lowers blood pressure and has been a recommended treatment option by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[3] However, in the recent National Institute for Health and Clinical Excellence hypertension guidelines, β blockers were no longer given first-line status because of concerns driven by outcomes data.[4] Concerns have also been raised by meta-analyses in which β blockers were reported to have a suboptimal effect on reducing stroke risk and increasing the risk for new-onset diabetes compared with other antihypertensive agents.[5,6] However, a closer examination of trials included in Lindholm et al's[5] meta-analysis revealed that the primary β blocker evaluated was atenolol, a traditional β blocker, and results for all other β blockers were insufficient for any definite conclusions. Moreover, the new-onset diabetes meta-analysis evaluated primarily atenolol, metoprolol, and propranolol, all β blockers without vasodilatory activity.[6] Vasodilatory activity may be a key contributor to advantageous outcomes in hypertension.[7] This review examines the current evidence supporting the use of β blockers in the treatment of hypertension, focusing on class diversity, recent vasodilatory β-blocker data, and compelling indications for β blockers.

Traditional β Blockers in the Treatment of Hypertension

There is a misconception that β blockers do not lower blood pressure equivalently to other classes of antihypertensive agents. However, the Blood Pressure Lowering Treatment Trialists' Collaboration meta-analysis reported that among 8 trials involving 37,872 patients comparing different classes of antihypertensive agents (angiotensin-converting enzyme [ACE] inhibitors, calcium antagonists, and β blockers and/or diuretics), blood pressure differences between treatment groups during follow-up (2 to 8 years) were minimal (systolic blood pressure [SBP] 0 to 3 mm Hg, diastolic blood pressure [DBP] $<$1 to 2 mm Hg).[8] Notably, β blockers were combined with diuretics as a single comparator group in the meta-analysis because of frequent concomitant use; the effects of β blockers alone were not reported. However, blood pressure reductions in large clinical trials comparing β blockers with diuretics showed no statistically significant differences between the 2 treatments, with approximately 3/4 of patients receiving either drug class achieving DBP goals.[9,10] It should be acknowledged that add-on therapy was more common with diuretics than with β blockers in these studies.

As noted in the National Institute for Health and Clinical Excellence guidelines, β blockers, primarily atenolol, were

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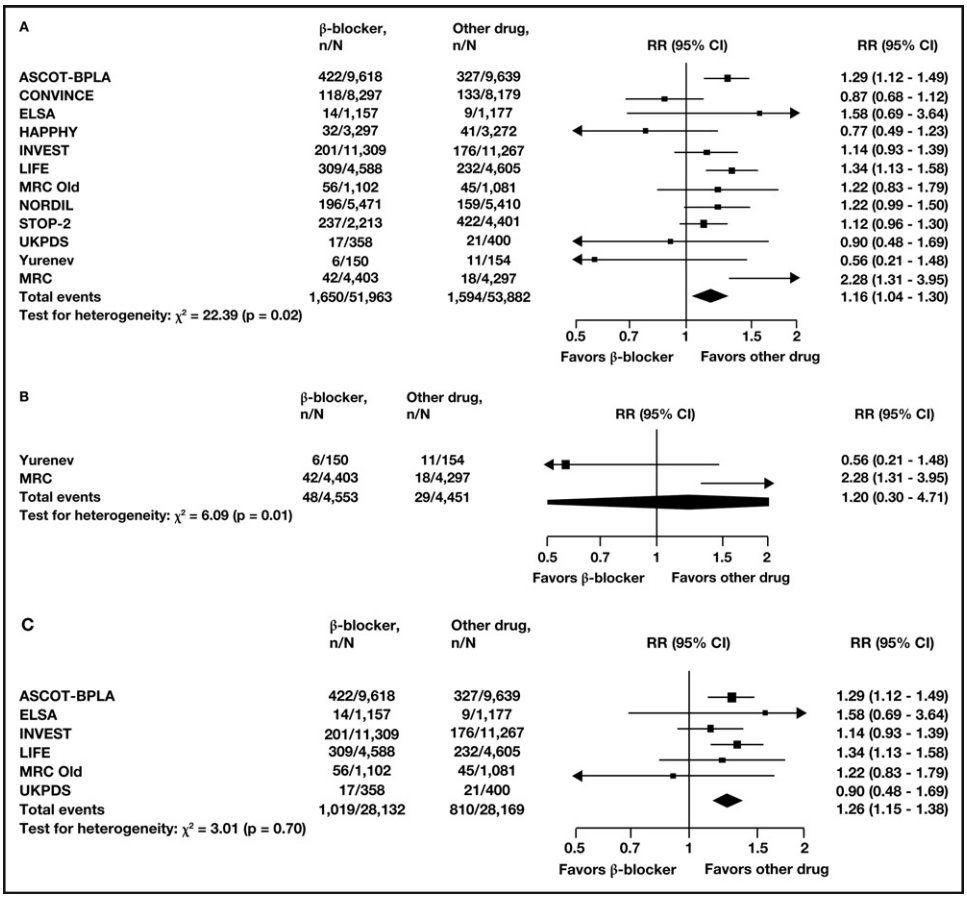

Figure 1. Stroke risk in trials that compared β blockers with other antihypertensive classes. *(A)* All β blockers versus other antihypertensive agents; *(B)* β blockers other than atenolol versus other antihypertensive agents; *(C)* atenolol versus other antihypertensive agents. ASCOT-BPLA = Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm; CI = confidence interval; CONVINCE = Controlled Onset Verapamil Investigation of Cardiovascular End Points; ELSA = European Lacidipine Study on Atherosclerosis; HAPPHY = Heart Attack Primary Prevention in Hypertension; INVEST = International Verapamil SR/Trandolapril Study; LIFE = Losartan Intervention for End Point Reduction in Hypertension; MRC = Medical Research Council; NORDIL = Nordic Diltiazem Study; RR = relative risk; STOP-2 = Swedish Trial in Old Patients With Hypertension 2; UKPDS = UK Prospective Diabetes Study. Reprinted with permission from *Lancet*.[5]

less effective than other classes of antihypertensive agents in reducing clinical complications, especially stroke.[4] However, to extrapolate these results to other agents in the β-blocker class is unwarranted, because there is a lack of quantitative evidence (i.e., outcomes data). In a meta-analysis of 7 trials involving 27,433 patients by Lindholm et al,[5] a reduction in stroke risk was reported with traditional β blockers, primarily atenolol, versus placebo or no treatment (about 19%). However, the risk reduction was not comparable with the reductions reported from 12 trials (9 trials with atenolol) involving 105,845 patients that compared ACE inhibitors, calcium antagonists, angiotensin receptor blockers (ARBs), and/or diuretics with β blockers (16% higher risk for β blockers, p = 0.009; Figure 1).[5] In contrast, differences in risk for myocardial infarction (relative risk 1.02, 95% confidence interval 0.93 to 1.12) and overall mortality (relative risk 1.03, 95% confidence interval 0.99 to 1.08) were not statistically significant between β blockers and other antihypertensive classes.[5] A limitation of this meta-analysis is that significant heterogeneity was present in the patient population. Another meta-analysis by Wang and Staessen[11] (9 trials involving 62,605 patients) reported no statistically significant difference between newer classes of antihypertensive agents (calcium channel blockers [CCBs], ACE inhibitors, and ARBs) and older agents (diuretics and β blockers) for cardiovascular mortality. A lack of substantial data from trials with β blockers other than atenolol would make it difficult to state broad outcome claims for β blockers as a class.

Traditional β blockers such as atenolol, metoprolol, and propranolol reduce blood pressure primarily via the reduction of cardiac output through chronotropic and inotropic inhibitory mechanisms.[12] However, reduced cardiac output can induce compensatory peripheral vasoconstriction to maintain blood pressure, which abets increased peripheral resistance, a hallmark of chronic hypertension.[12] An increase in systemic vascular resistance diminishes blood flow to peripheral tissues, such as the skeletal muscles, and may lead to adverse effects on lipid and glucose metabolism, which in turn contribute to the development of endothelial dysfunction and diabetes.[12,13]

Although traditional β blockers effectively lower brachial (arm) blood pressure, recent clinical data suggest that they may have less effect on reducing central aortic pressure

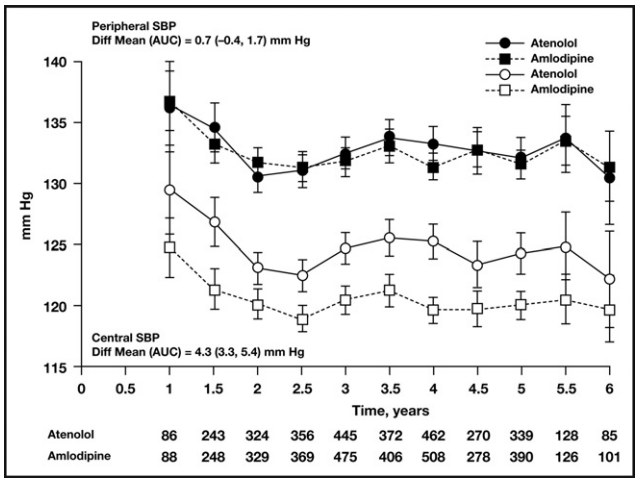

Figure 2. Brachial and derived central aortic SBP in patients receiving either atenolol- or amlodipine-based therapy. Time represents the duration from randomization to the patient follow-up visit, during which a tonometry measurement was performed. AUC = area under the curve. Adapted with permission from *Circulation*.[16]

compared with other antihypertensive classes.[14–16] In the Conduit Artery Function Evaluation (CAFE), a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), central aortic pressure and brachial SBP were evaluated in 2,199 patients with hypertension and ≥3 other cardiovascular risk factors.[16] Despite a difference of only 0.7 mm Hg in brachial SBP reduction between the amlodipine-based and atenolol-based therapy, favoring amlodipine, central aortic SBP was decreased by 4.3 mm Hg with amlodipine compared to atenolol ($p < 0.0001$; Figure 2).[16–18] Because increased central aortic pressure has been associated with an increased risk for vascular events, especially stroke,[19] these results may at least partially explain the residual stroke risk associated with traditional β blockers.

Vasodilatory β Blockers in Treating Hypertension

Vasodilatory β blockers decrease blood pressure largely through reducing systemic vascular resistance, while maintaining cardiac output.[12,20] The benefits of peripheral vasodilation contribute to reduced cardiac afterload and preload, lack of adverse effects on lipid and glucose metabolism, and possible reversal of adverse arterial remodeling.[12,20,21] Arterial remodeling (stiffness) may increase distal wave reflection of blood back to the aorta, which augments the outgoing central systolic pulsewave from the heart, thus increasing central aortic pressure.[20] Reversal of arterial remodeling may thereby lower central aortic pressure. By lowering blood pressure in a more physiologically relevant manner, vasodilatory β blockers may be a more appropriate therapy for hypertension compared with traditional β blockers (Table 1).[12]

Labetalol: Labetalol is a nonselective β locker with α_1 receptor–blocking activity and minimal intrinsic sympathomimetic activity.[20] Labetalol lowers blood pressure rapidly (orally, within 2 hours; intravenously, within 5 minutes) and therefore has been useful in hypertensive emergencies.[22,23] A randomized, double-blind, placebo-controlled clinical trial in 74 patients with mild hypertension showed that labetalol (600 mg/day) effectively lowered supine and standing blood pressure compared to placebo ($p < 0.05$).[24] In 134 patients with moderate to severe hypertension (DBP 105 to 129 mm Hg), open-label labetalol (100 to 400 mg/day for up to 18 weeks) effectively lowered standing blood pressure from baseline (−32.9/−20.4, $p < 0.001$ for both) with 75% of patients achieving goal blood pressure (DBP ≤90 mm Hg).[25] Labetalol was generally well tolerated in these clinical studies. On the basis of data from small clinical trials, labetalol was equally effective in lowering SBP and more effective in lowering 24-hour DBP compared to a CCB or an ACE inhibitor.[26,27]

Carvedilol: Carvedilol is a nonselective β blocker with α_1 receptor–blocking activity and no intrinsic sympathomimetic activity.[20] Clinical data suggest that carvedilol reduces systemic vascular resistance in patients with hypertension.[28,29] Carvedilol was originally formulated for twice-daily administration; however, a bioequivalent, once-daily, controlled-release carvedilol formulation is now available for the same clinical indications (hypertension, heart failure, and post–myocardial infarction left ventricular dysfunction).[30] In a placebo-controlled, double-blind trial in 338 patients with essential hypertension randomized to controlled-release carvedilol 20, 40, or 80 mg or placebo once daily for 6 weeks, each controlled-release carvedilol dose significantly lowered mean 24-hour SBP and DBP assessed by ambulatory blood pressure monitoring compared with placebo ($p \leq 0.001$ for all).[31] Blood pressure reductions were dose dependent and maintained throughout the dosing interval (Figure 3).[31] Controlled-release carvedilol was generally well tolerated, with an overall similar low incidence of emergent adverse events as observed with placebo.

Nebivolol: Nebivolol is a β_1-selective β blocker that does not have α_1-blocking activity or intrinsic sympathomimetic activity.[20] Clinical data suggest that nebivolol reduces systemic vascular resistance in patients with hypertension, possibly through stimulation of nitric oxide release.[20,32] A recent randomized, double-blind, placebo-controlled trial in 909 patients with mild to moderate hypertension showed that nebivolol 1.25 to 40 mg/day effectively lowered SBP and DBP compared to placebo after 84 days of treatment ($p \leq 0.002$ and $p < 0.001$, respectively, for all doses; Figure 4).[33] In an open-label, 6-week trial in 6,356 patients with mild hypertension (defined as DBP of 90 to 115 mm Hg) and mean baseline SBP of 162 mm Hg, nebivolol (5 to 10 mg/day) significantly lowered mean SBP and DBP from baseline (−24 and −13 mm Hg, respectively, $p < 0.001$ for both).[34] Nebivolol (2.5 to 10 mg/day) was also assessed as monotherapy or as add-on therapy in 2,838 patients with hypertension and type 2 diabetes mellitus for ≥3 months and lowered SBP and DBP from baseline by 21 and 11 mm Hg, respectively.[35] Although most patients receiving nebivolol 5 mg/day achieved blood pressures ≤140/90 mm Hg, only 9.6% of patients achieved the goal blood pressure recommended for patients with diabetes (<130/80 mm Hg).[34] Nebivolol was generally safe and well tolerated. Nebivolol had comparable efficacy with other β

Table 1
Effects of antihypertensive drugs in hypertension

Effect	Ideal Drug	Traditional β Blocker	Vasodilating β Blocker	α_1 Adrenoceptor Blocker	ACE Inhibitor/ARB	DHP Calcium Antagonist	Thiazide Diuretic
Mean arterial blood pressure	↓	↓	↓	↓	↓	↓	↓
Total peripheral resistance	↓	(↑)	(↓)	↓	↓	↓	↓
Cardiac output	0	(↓)	0	0	0	0	0
Heart rate	0/↓	↓	0/↓	(↑)	0	(↑)	0
SNS activation	↓	↓	↓	(↑)	↓	↑	↑
RAS	↓	↓	↓	0	↓	↑	↑
Lipid metabolism	0/+	−	0	0/+	0	0	−
Glucose metabolism	0/+	−	0	0	0/+	0	−

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DHP = dihydropyridine; SNS = sympathetic nervous system; RAS = renin-angiotensin system; ↑ = increase (activation); ↓ = decrease (inhibition); 0 = no effect; + = positive effect; − = negative effect; ( ) = predominantly after acute administration.

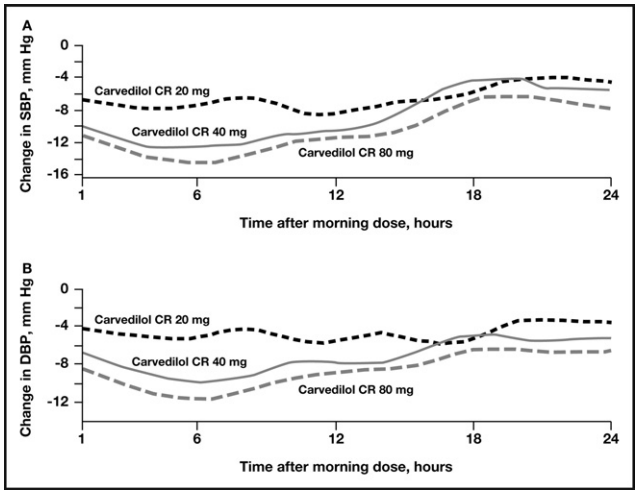

Figure 3. Effects of controlled-release (CR) carvedilol in patients with hypertension. *(A)* SBP and *(B)* DBP in patients receiving CR carvedilol 20, 40, or 80 mg. Values represent changes from baseline at 6 weeks as measured by 24-hour ambulatory monitoring. Lines were smoothed using locally weighted regression. Data from *J Clin Hypertens (Greenwich)*.[31]

blockers and antihypertensive agents.[36–38] In a meta-analysis of 12 randomized clinical trials in patients with hypertension, achievement of blood pressure targets or goal reductions with nebivolol was higher than that of ACE inhibitors (odds ratio 1.92, p = 0.001) and similar to that of other β blockers, CCBs, and losartan.[38]

Use of β Blockers in Patients With Hypertension and Other Compelling Indications

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends β blockers for the treatment of hypertension, particularly in patients with certain compelling indications, such as diabetes, high coronary disease risk, and heart failure, or in patients who have experienced myocardial infarctions.[3] In these particular conditions, the effects of β blockers on the myocardium itself may provide benefits beyond lowering blood pressure.[39]

Diabetes: Although traditional β blockers have been effective in patients with diabetes, the adverse metabolic and lipid consequences raise some concerns.[12] The new-onset diabetes risk with traditional β blockers in clinical trials is variable, depending on dose, treatment duration, and patient age.[6] A recent meta-analysis by Bangalore et al[6] of 12 trials involving 94,492 patients with hypertension reported a 44% increased new-onset diabetes risk with pooled data of the traditional β blockers atenolol and propranolol compared with placebo (n = 16,372, p = 0.33). Compared with thiazide diuretics, atenolol, metoprolol, and propranolol (n = 8,980) were associated with a 26% lower new-onset diabetes risk (p = 0.002).[6] Compared with CCBs and ACE inhibitors or ARBs, β blocker–based therapy (atenolol, metoprolol, and any β blocker and diuretic together) increased the new-onset diabetes risk by 21% and 23%, respectively (p <0.0001 and p = 0.007, respectively).[6] However, several limitations should be considered when evaluating the results of this meta-analysis: marked heterogeneity was present in the comparisons except for the ACE inhibitors and ARBs, most patients were receiving >1 antihypertensive agent by trial end, and the diagnostic diabetes criteria were not uniform across the trials, making it difficult to compare incidence rates accurately.

In contrast, vasodilatory β blockers such as carvedilol and nebivolol have shown neutral or beneficial effects on metabolic parameters in patients with diabetes and hypertension (Table 1).[12,35,40] In the Glycemic Effect in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial (n = 1,235), carvedilol (6.25 to 25.0 mg twice daily) demonstrated efficacy in reducing blood pressure comparable toh the traditional β blocker metoprolol tartrate (50 to 200 mg twice daily), without adversely affecting glycemic control in patients who were receiving ACE inhibitors or ARBs.[40,41] At study end, carvedilol lowered SBP and DBP to the same extent as metoprolol.[40] However, the discontinuation rate because of poor glycemic control was 2.2% with metoprolol but only 0.6% with carvedilol (p = 0.04). Additionally, carvedilol had no adverse effect on glycosylated hemoglobin values (mean change from baseline 0.02%, 95% confidence interval −0.06 to 0.10).[41] In a subgroup analysis in another trial, glycosylated hemoglobin was significantly reduced from baseline with nebivolol (n = 1,485; 6.93% vs 6.68% after treatment, p < 0.001).[35] There was also a significant decrease from baseline in fasting glucose (n = 1,644; 135.1 vs

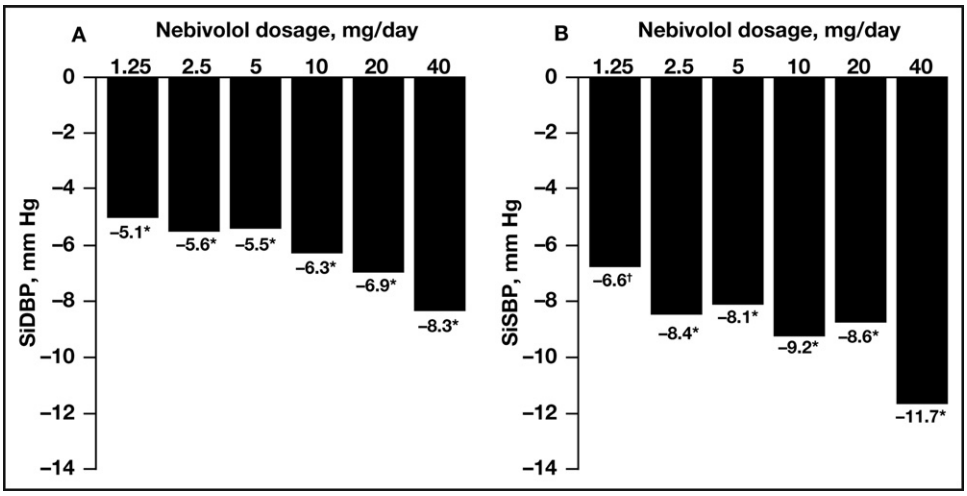

Figure 4. Placebo-subtracted least-squares mean reductions in trough sitting DBP (SiDBP) in patients with hypertension. *(A)* Trough SiDBP and *(B)* trough sitting SBP (SiSBP) from baseline to study end in nebivolol-treated patients with hypertension. *p <0.001 versus placebo, †p = 0.002 versus placebo. Reproduced with permission from *J Clin Hypertens (Greenwich)*.[33]

122.0 mg/dl after treatment, p <0.001). These results suggest a lack of adverse effect on glycemic control with nebivolol; however, interpretation is limited by the open-label study design that did not include a placebo or active comparator.

Coronary artery disease: Coronary artery disease is characterized in part by reduced myocardial oxygen supply when demand is high.[3] Reduction of blood pressure, heart rate, and myocardial oxygen demand in patients with coronary artery disease reduces ischemia and lowers the risk for cardiovascular events.[3] The American Heart Association recommends a blood pressure goal of <130/80 mm Hg for patients diagnosed with coronary artery disease, with conditions considered coronary artery disease risk equivalents (i.e., carotid artery disease, peripheral artery disease, abdominal aortic aneurysm), or at high risk for developing coronary artery disease (10-year Framingham risk score ≥10%).[42]

Treatment of coronary artery disease with β blockers is recommended by several guidelines because β blockers not only reduce blood pressure but also decrease myocardial oxygen demand.[3,42] However, the effects of nonvasodilating β blockers on hyperemic coronary blood flow are variable, which may or may not increase coronary flow reserve.[43] Reduction of coronary flow reserve via increased coronary blood flow at rest or decreased hyperemic coronary blood flow is an independent, negative factor for mortality in patients with coronary artery disease.[43] Because of amelioration of rest and hyperemic coronary blood flow, vasodilatory β blockers may be a better option than traditional β blockers in patients with high coronary artery disease risk[43] (Table 1).[12] It should be noted, however, that no vasodilating β blockers currently have an indication for the treatment of chronic stable angina in patients with coronary artery disease.

Post–myocardial infarction: According to American Heart Association guidelines, β blockers are recommended in hemodynamically stable hypertensive patients after myocardial infarction.[42] The value of β blockers in patients after myocardial infarction has been established in the β-Blocker Heart Attack Trial (BHAT; propranolol), the Gothenburg metoprolol trial, the Norwegian timolol trial, and the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial.[44–47] Among the vasodilatory β blockers, only carvedilol is indicated for use in patients with post–myocardial infarction left ventricular dysfunction.[48]

Heart failure: Heart failure is a serious natural progression of uncontrolled hypertension.[49] Beta blockers, specifically bisoprolol, metoprolol succinate, and carvedilol, improve outcomes in patients with systolic heart failure by inhibiting the negative effects associated with sympathetic nervous system activation.[50] Benefits of β-blocker therapy in this patient population include reducing the risk for death and reducing symptoms, improving clinical status, and improving overall patient well-being. Moreover, recent clinical evidence suggests that the risk for mortality and rehospitalization are significantly lower in patients with heart failure who continue β-blocker therapy after hospital discharge compared to patients not continuing β-blocker treatment (p = 0.012).[51]

Carvedilol (6.25 to 25 mg twice daily) was shown to significantly reduce the all-cause mortality risk by 17% compared to metoprolol tartrate (50 mg twice daily) (p = 0.002) in patients treated with diuretics and ACE inhibitors in the Carvedilol or Metoprolol European Trial (COMET).[52] Furthermore, carvedilol reduced the risk for cardiovascular death by 20% and stroke death by 67% compared to metoprolol (p <0.001 for both).[52,53] Nebivolol (1.25 to 10 mg/day) was shown to significantly reduce the combined risk for all-cause mortality or cardiovascular-related hospital admission by 14% compared to placebo (p = 0.039) in the Study of the Effects of Nebivolol Intervention of Outcomes and Rehospitalisation in Seniors With Heart Failure (SENIORS).[54,55] However, all-cause mortality alone was not reduced versus placebo (p = 0.214). Nebivolol does not currently have a heart failure indication in the United States.

Are β Blockers Effective in Treating Hypertension?

The review of the evidence provided herein confirms that there are valid reasons to question the utility of certain β blockers in treating hypertension. However, many of the perceptions about β blockers are derived from data obtained from studies of traditional agents or combinations of diuretics and β blockers. Evidence suggests, and the guidelines concur, that there are intrinsic differences among members of the β-blocker class. Indeed, the vasodilatory β-blockers, which have generally not been included in comparative meta-analyses, lower blood pressure to a similar degree as other antihypertensive drugs, may provide better central aortic pressure reductions than traditional β blockers, and are associated with neutral or favorable metabolic effects.

The reality of modern hypertension treatment is that most patients will require multiple drugs to achieve blood pressure goals. In patients with co-morbidities that necessitate more aggressive goals, combination therapy will likely be essential. For many of these patients, including those with diabetes or high coronary artery disease risk, β blockers are a beneficial, guideline-recommended treatment option. Therefore, when addressing the question of β blockers' effectiveness, the answer lies not in global generalizations but in assessing individual patients and specific β-blocking agents.

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