The Vasodilatory Beta-blockers

Michala E. Pedersen, DPhil, MRCP, and John R. Cockcroft, MD, FRCP

Corresponding author
John R. Cockcroft, MD, FRCP
Department of Cardiology, Wales Heart Research Institute, Cardiff University, Heath Park, Cardiff CF14 4XN, UK.
E-mail: cockcroftjr@cf.ac.uk

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Although well established in treating hypertension and cardiovascular (CV) disease, clinical trial data suggest that β-blockers (eg, atenolol) may be less effective than other antihypertensive classes in reducing stroke and CV mortality despite similar blood pressure (BP) reductions. One possible explanation is that atenolol is less effective in reducing central aortic pressure. Newer vasodilating β-blockers may prove more effective in reducing central pressure and cardiovascular events. Carvedilol and labetalol appear to cause vasodilation through α_1-receptor blockade; nebivolol induces endothelium-dependent vasodilation by stimulating nitric oxide bioactivity. Their favorable hemodynamic profile includes reduction of peripheral vascular resistance (PVR) while maintaining or improving cardiac output (CO), stroke volume, and left ventricular function, whereas nonvasodilating β-blockers tend to raise PVR and reduce CO and left ventricular function. Compared with conventional β-blockers, vasodilating β-blockers have beneficial hemodynamic effects including decreased pressure wave reflection from the periphery, leading to decreases in central aortic blood pressure. Larger trials are needed to determine whether reduced central pressure will translate into improved CV outcomes compared with nonvasodilating β-blockers.

Introduction

Of the classes of antihypertensive agents currently available for clinical use, β-blockers are among the oldest and most widely used. After more than 40 years of clinical experience with these drugs, β-blockers are proven to be effective in reducing blood pressure (BP), and are particularly recommended for many high-risk patients with coronary artery disease (CAD), post-myocardial infarction (MI), heart failure (HF), and diabetes [1]. Although β-blockers are known to suppress norepinephrine and overactivity of the sympathetic nervous system, the precise mechanisms by which they lower BP and provide cardioprotection are still incompletely understood [2]. The clinical benefits of β-blockers are believed to derive from a reduction in heart rate (HR), cardiac output (CO), and myocardial oxygen demand; an increase in diastolic filling time of the coronary arteries; suppression of excessive renin release; and antiarrhythmic properties to prevent sudden death [2].

However, β-blockers are very heterogeneous in their pharmacologic properties and hemodynamic effects [2]. For example, β-blockers vary greatly in their degree of selectivity for the β_1-adrenergic receptor, lipophilicity, intrinsic sympathomimetic activity, membrane-stabilizing action, and vasodilatory properties [2]. The heterogeneity of the β-blocker class, and the clinical implications of these differences, have become especially important in view of recent analyses that question the ability of some β-blockers to reduce the risks of stroke and other cardiovascular (CV) events in hypertensive patients, the ultimate goal of treatment. This review assesses the data comparing vasodilatory β-blockers with conventional nonvasodilating β-blockers, and the clinical implications of these findings.

The β-blocker Controversy

Despite the well-established antihypertensive and cardioprotective benefits of β-blockers, their appropriate use in the general hypertensive population has become controversial, based primarily on recent findings. A large meta-analysis by Lindholm et al. [3••] (20 trials; N = 133,384) showed that although β-blocker therapy significantly reduced the risk of stroke by 19% in hypertensive patients, compared with placebo, this decrease was less than the risk reduction seen with other classes of agents. The ASCOT-BPLA study found that a regimen of amlodipine adding perindopril as required reduced the risk of CV events to a greater degree than treatment with atenolol adding a thiazide diuretic as required after a 5.5-year median follow-up in 19,257 patients with hypertension and other CV risk factors [4••]. Although the amlodipine-based regimen achieved a mean 2.7 mm Hg greater BP reduction than treatment with the atenolol-based regimen, this difference was considered insufficient to explain the disparities in reduction of CV risk [4••].

The data from the Lindholm et al. [3••] meta-analysis and the ASCOT-BPLA study [4••] led the National Institute for Health and Clinical Excellence (NICE) and the British Hypertension Society (BHS) in the United Kingdom to

remove β-blockers as first-line agents from their recommended list of agents for treatment of uncomplicated hypertension, although both organizations reaffirmed that these agents remain preferred therapies for specific indications such as MI and HF [5]. The NICE-BHS guidelines caution, however, that this conclusion may not extend to all β-blockers given the paucity of data for β-blockers other than atenolol [5]. Indeed, atenolol has commonly been used as the reference agent for β-blocker therapy in clinical trials [6]. In the analysis by Lindholm et al. [3••], for example, the data comparing β-blockers other than atenolol with drugs of other antihypertensive classes included too few events for analysis.

The efficacy of β-blockers may be stratified by age, because BP in older patients is characterized by reduced arterial compliance. In contrast, hypertension in younger patients is often associated with increased sympathetic drive and CO [7]. A meta-analysis of 21 hypertension trials in 145,811 patients found that initial treatment with β-blockers provided less protection against stroke only in patients 60 years of age or older, and afforded similar protection in patients younger than 60 years (N = 30,412) compared with other classes of antihypertensive agents [7]. Based on these data, the current guidelines from the Canadian Hypertension Education Program recommend β-blockers as an appropriate first-line therapy in hypertensive patients younger than 60 years [8].

The question remains, however, whether clinical trial data based on atenolol can be extrapolated to other β-blockers [5]. A meta-analysis that included only atenolol trials (nine studies; N = 24,496) confirmed that mortality was significantly higher with this agent, despite similar reductions in BP, compared with other antihypertensive drugs [6]. Researchers have postulated that physiologic mechanisms other than BP reduction, as conventionally measured, may explain this disparity [3••,9•]. A better understanding of these mechanisms may also help predict whether vasodilating β-blockers are likely to have beneficial effects on CV outcomes compared to atenolol.

Hemodynamic Effects of Atenolol

Although conventionally measured at the brachial artery, BP varies considerably throughout the arterial tree [10]. Brachial artery BP is a strong predictor of CV risk, but the heart and brain are directly exposed to central aortic pressure [10]. Antihypertensive agents also vary in their effects on central aortic pressure, despite similar effects on brachial artery BP [9•]. It was hypothesized, therefore, that the disparity in CV risk reduction between conventional β-blockers and other classes of antihypertensive agents may be related to their respective effects on central aortic pressure [9•].

The CAFE study (N = 2199), which was a substudy of ASCOT-BPLA, was the first major trial designed to evaluate this hypothesis [9•]. After up to 4 years of follow-up, central aortic systolic and pulse pressures were significantly lower with therapy of amlodipine adding perindopril as required, compared with the regimen of atenolol adding thiazide as needed ($P < 0.0001$ for both systolic and pulse pressures), despite similar reductions in peripheral brachial BP. In addition, therapy with amlodipine adding perindopril as needed was associated with significantly lower central aortic systolic pressure and augmentation index (the central aortic systolic pressure wave attributable to wave reflection), compared with treatment with atenolol adding thiazide as needed ($P < 0.0001$ for both parameters). Central aortic diastolic pressure was also lower with treatment with amlodipine adding perindopril as needed ($P < 0.001$), although this difference was not as great as in central aortic systolic pressure. Increased central aortic pulse pressure and augmentation index have been significantly and independently associated with risk of CV events in patients with CAD [11,12].

A smaller study in 21 patients with never-treated hypertension demonstrated results similar to those of CAFE [13]. In this 6-week study, the angiotensin II–receptor blocker (ARB) eprosartan induced significantly greater reduction of central systolic pressure ($P = 0.03$) and central systolic wave augmentation index ($P < 0.001$), compared with atenolol, although both drugs produced similar reductions in peripheral BP. Atenolol reduced aortic pulse wave velocity (PWV) significantly more than did eprosartan ($P = 0.005$).

It is unclear why conventional β-blockers have reduced efficacy in lowering central aortic systolic pressure. The CAFE researchers noted that because the atenolol with or without thiazide-based therapy in their study did not increase central aortic systolic pressure wave magnitude, the significant increases in central systolic pulse wave augmentation were apparently due to greater distal wave reflection [9•]. They further suggested that the reduced HR induced by atenolol prolonged systolic ejection time and delayed the peak of the outgoing wave, causing the pressure wave reflections to augment the central aortic systolic pressure wave. Therefore, the effects of vasodilating β-blockers on these hemodynamic factors could have a bearing on their effects on central aortic systolic pressure.

Vasodilating β-blockers

The chief vasodilating β-blockers—betaxolol, carteolol, carvedilol, celiprolol, labetalol, nebivolol, and nipradilol—have varying pharmacologic properties and mechanisms of vasodilation; because they are relatively new, not all have been approved for use in the United States [14]. Carvedilol and labetalol have been approved for use by the US Food and Drug Administration (FDA), and nebivolol is currently under FDA review for use in the treatment of hypertension [15,16]. This review examines the major properties and actions of these agents likely to be of particular interest to US physicians.

Hemodynamic benefits of vasodilation

The hemodynamic benefits of arterial and venous vasodilation include reduction of peripheral vascular resistance (PVR) and myocardial afterload and preload, thereby decreasing cardiac work and myocardial oxygen demand [14]. These actions may also be important in reversing pathogenic hypertensive CV remodeling. Literature reviews have established that vasodilating antihypertensive agents, regardless of vasodilatory mechanism, reverse remodeling of resistance artery structure, whereas this benefit is not observed with nonvasodilating β-blockers, independent of BP reduction [17].

Vascular remodeling of the small arteries, usually measured as an increased media-to-internal lumen ratio, is associated with increased PVR (a hallmark of essential hypertension), reduced coronary vasodilator capacity and flow reserve, and increased risk of CV events [18]. Vasodilatory antihypertensive therapy improves coronary flow reserve, whereas conventional β-blockade with atenolol does not [19]. Moreover, hypertensive remodeling of resistance arteries and endothelial dysfunction contributes to the increased distal wave reflection that leads to central systolic pulse wave augmentation [20••]. The decrease in HR with β-blockade may contribute to increased central systolic pulse wave augmentation [9•]. However, vasodilation with β-blockade could, hypothetically, counteract the deleterious effect of slowed HR by reversing small artery remodeling and endothelial dysfunction, thereby decreasing distal wave reflection.

Therapeutic vasodilation may thus enhance the antihypertensive benefits of β-blockade and offset its drawbacks, including increased PVR and negative cardiac inotropy [14]. Yet the mechanisms and extent of vasodilation vary significantly among β-blockers [14].

Carvedilol

Carvedilol, a highly lipophilic nonselective β-blocker, competitively blocks the β_1, β_2, and α_1 receptors and has no intrinsic sympathomimetic activity (ISA) [21]. The primary mechanism of carvedilol's vasodilating action is α_1-receptor blockade [21]. Experimental findings suggest that carvedilol's antihypertensive action may also be partly dependent on stimulation of endothelial nitric oxide (NO) [22]. However, carvedilol has also demonstrated direct anti-NO actions, and its overall effect on NO-bioactivity remains unclear [23].

In patients with hypertension, carvedilol has demonstrated reductions in BP, exercise and resting HR, and cardiac index, accompanied by mildly decreased PVR and increased exercise stroke index [21]. Carvedilol did not cause the increases in PVR and capillary wedge pressure or the decrease in CO observed with propranolol in patients with CAD [24], and demonstrated no change in PVR, compared with a decrease with metoprolol, in hypertensive patients [25]. Carvedilol has also been reported to improve left ventricular (LV) structure and function in patients with hypertension and with HF [21]. Overall, carvedilol has demonstrated less reduction of HR at rest or following exercise, less increase in post-exercise BP, and maintenance or a slight increase in CO, compared with conventional β-blockers [26].

Labetalol

Labetalol is a lipophilic nonselective β-blocker that competitively blocks the β_1, β_2, and α_1 receptors and has minimal ISA [27,28]. The vasodilatory mechanism of labetalol is unclear and the presence of vasodilation with this agent has been problematic [14]. However, compared with conventional β-blockers, labetalol has demonstrated a distinct and favorable hemodynamic profile, including reduction of PVR and minimal change in HR and CO, suggesting peripheral vasodilation, as well as regression of vascular remodeling, in hypertensive patients [27,29,30]. Labetalol is believed to cause vasodilation in part through α_1-receptor blockade [29]. The effect of labetalol on NO is not well studied.

Nebivolol

Nebivolol, a highly lipophilic agent with no ISA, has the highest selectivity to the β_1-adrenergic receptor among other commonly prescribed β-blockers [15,31]. Extensive data have established that nebivolol produces endothelium-dependent vasodilation through stimulation of the L-arginine/NO pathway [15,32•]. In healthy volunteers, nebivolol increased forearm blood flow (FBF), a measure of brachial artery vasodilation, by 91% ($P < 0.01$), compared with baseline; conversely, atenolol had no effect [33]. Nebivolol also increased FBF in hypertensive patients ($P = 0.0003$) compared with baseline [34]. Oral administration of nebivolol 5 mg once daily plus bendrofluazide 2.5 mg once daily for 8 weeks significantly improved FBF in response to acetylcholine, compared with baseline ($P < 0.001$), whereas atenolol 50 mg once daily plus bendrofluazide had no effect on FBF (Fig. 1) [35].

Nebivolol thus appears to reverse endothelial dysfunction, which may contribute to reduction of distal wave reflection and central systolic augmentation [9•,35]. Because endothelium-derived NO has been shown to regulate arterial stiffness [36], an independent predictor of CV outcome, drugs that potentiate NO may be particularly effective in reducing CV events [37]. Infusion of nebivolol in the common iliac artery of sheep significantly reduced PWV ($P < 0.05$ and $P < 0.01$ with doses of 250 and 500 nmoL/min, respectively), compared with baseline, whereas atenolol had no significant effect on PWV [38]. As with the vasodilatory effects of nebivolol, its effect on PWV is also NO dependent, as it can be inhibited by N^G-monomethyl-L-arginine.

Nebivolol has also demonstrated a favorable hemodynamic profile, clearly distinct from that of conventional β-blockers. In healthy volunteers, nebivolol demonstrated no impairment of exercise capacity, compared with significant decreases in exercise capacity with atenolol, pindolol,

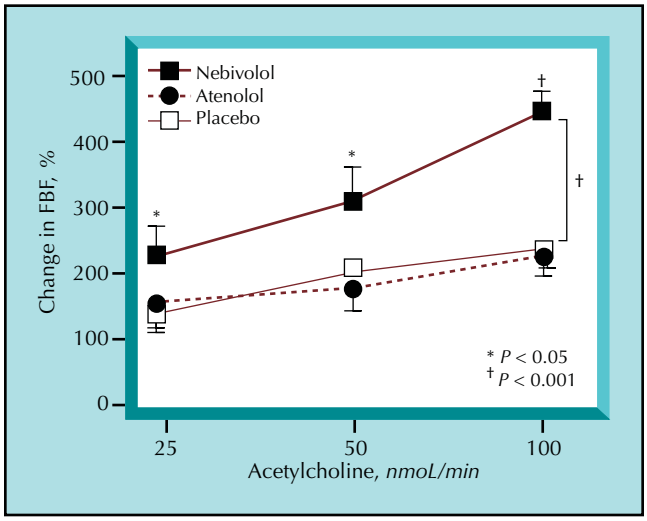

Figure 1. In 12 patients with hypertension, double-blind, randomized treatment for 8 weeks with nebivolol 5 mg plus bendrofluazide 2.5 mg once daily significantly increased vasodilatory response to acetylcholine as indicated by forearm blood flow (FBF), compared with crossover treatment with atenolol 50 mg plus bendrofluazide 2.5 mg once daily. *Asterisk* indicates $P < 0.05$; *dagger* represents $P < 0.001$. (*Modified from* Tzemos et al. [35].)

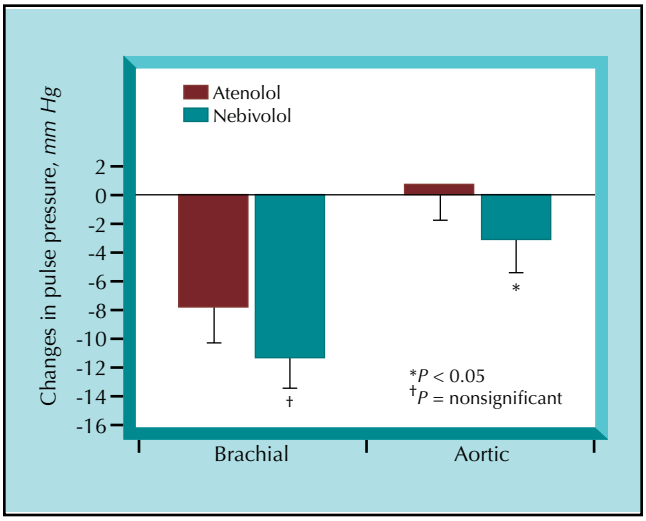

Figure 2. Effects of atenolol and nebivolol on brachial and central aortic pulse pressure. After 5 weeks of placebo-controlled, double-blind, crossover treatment with atenolol and nebivolol in 16 never-treated patients with hypertension, the placebo-corrected reduction in brachial pulse pressure was similar between the two agents, but central aortic pulse pressure was significantly lower with nebivolol (50 + 2 mm Hg vs 54 + 2 mm Hg). *Asterisk* indicates $P < 0.05$; *dagger* represents P = nonsignificant. (*Modified from* Wilkinson et al. [Personal communication, February 2007].)

and propranolol [16,39]. In patients with essential hypertension, nebivolol 5 mg once daily for 2 weeks reduced HR to a significantly lesser degree than atenolol 100 mg once daily, and significantly reduced PVR, increased stroke volume, and slightly increased CO; atenolol, in contrast, was associated with small increases in mean stroke volume and peripheral resistance and a significant reduction in CO [39]. Nebivolol 5 mg once daily for 4 weeks also induced a significant increase in coronary flow reserve ($P < 0.0001$) in hypertensive patients without known CAD [40].

Nebivolol has consistently demonstrated preservation or improvement of LV structure and function in healthy and hypertensive patients, and in patients with cardiomyopathy, CAD, and HF [16]. In patients with HF, for example, nebivolol improved or maintained cardiac index and stroke volume to a greater degree than atenolol [16].

Nebivolol and central blood pressure

A recent double-blind, randomized, crossover study in 16 never-treated hypertensive subjects, conducted by Ian Wilkinson et al. (Personal communication, February 2007), showed that nebivolol and atenolol produced similar reductions in brachial BP, but nebivolol lowered aortic BP by 4.0 mm Hg more than atenolol (Fig. 2). This difference in aortic BP was similar to the reduction observed in the CAFE study between the atenolol/bendrofluazide and amlodipine/perindopril treatment arms. Further study is needed on this important possible distinction between vasodilatory and nonvasodilatory β-blockers.

Antioxidant and antiproliferative actions

Vasodilating β-blockers have generally demonstrated significant antioxidant and antiproliferative effects [14,16,26]. Labetalol inhibited production of reactive oxygen species (ROS) by neutrophils and reduced the risk of lipid peroxidation, compared with no such effects seen with conventional β-blockade during in vitro and ex vivo studies [41,42]. Data are lacking on the effects of labetalol on vascular cell proliferation.

The antioxidant properties of nebivolol and carvedilol are associated with stimulation and release of NO [14,37]. Carvedilol has demonstrated significant protection against ROS activity in multiple human and animal cell models of lipoprotein and oxidation and endothelial cell injury [21]. The antioxidant actions of carvedilol appear to include both scavenging of free radicals and sequestration of ferric ion to prevent ferric ion-induced oxidation [14]. In clinical studies, carvedilol has significantly reduced lipid peroxidation, oxidative stress, ischemic target organ injury, and antiatherosclerotic actions in patients with hypertension, ischemic heart disease, heart failure, and diabetes [14]. Carvedilol also demonstrated suppression of endothelin-1 in human endothelial cells, in contrast to metoprolol, propranolol, and other antihypertensive drugs, which had no effect; this action may be an important mechanism of carvedilol's antioxidant effect [43].

Nebivolol has demonstrated significant inhibition of ROS activity and NO synthase uncoupling in a variety of experimental models of hypertension, hyperlipidemia, and atherosclerosis [37,44]. Nebivolol increased the ratio of NO to peroxynitrite, a highly reactive and toxic molecule, in spontaneously hypertensive rats, compared with no effect with atenolol [37]. In human endothelial cells from age-matched black and white donors, nebivolol reduced

superoxides and peroxynitrite while increasing NO bioactivity [45]. In clinical studies, nebivolol significantly lowered indicators of oxidative stress in healthy volunteers [16]; and in hypertensive patients it significantly lowered plasma malondialdehyde ($P = 0.03$) and significantly increased adiponectin levels ($P = 0.04$), compared with metoprolol [46]. Nebivolol also significantly lowered lipid peroxidation, ROS, and superoxide, compared with atenolol, in patients with hypertension [47].

Both nebivolol and carvedilol reduced proliferation of human coronary endothelial and smooth muscle [14,21]. Nebivolol appears to prevent vascular smooth muscle cell growth via stimulation of NO and interference with cell cycle regulatory signaling [48]. Carvedilol also inhibited endothelin-1 stimulated mitogenic response in rat aortic vascular smooth muscle cells, whereas labetalol and conventional β-blockers did not share this effect [49].

Clinical Effects

Blood pressure reduction

In clinical trials, carvedilol, labetalol, and nebivolol have lowered BP to a similar extent as conventional β-blockers and agents of other antihypertensive drug classes [15,21,26,50]. Labetalol is distinguished as a rapid-acting drug recommended for use in hypertensive emergencies [50]. Of particular interest, however, is the antihypertensive efficacy of vasodilating β-blockers in special populations known to have a reduced response to conventional β-blockers, including the elderly and blacks [2]. In patients 60 years of age or older with hypertension, labetalol has demonstrated significant reduction of systolic and diastolic BP, compared with placebo ($P < 0.01$), an effect similar to that in patients younger than 60 years of age [51]. Labetalol also demonstrated equal antihypertensive efficacy in black and white patients with hypertension, and greater efficacy than propranolol in black patients [52].

Few such data in special populations are available for carvedilol monotherapy. A large observational study of nebivolol monotherapy in patients with hypertension ($N = 6376$) found that the rate of response in patients older than 65 years and older than 75 years (92.9% in both) was similar to that in patients younger than 65 years (92.8%) [53]. In addition, a large, randomized, placebo-controlled, dose-ranging study ($N = 509$) found that nebivolol had similar efficacy in hypertensive black patients as in white patients, with average BP reductions at trough of -9.7/8.5 mm Hg and -9.0/9.4 mm Hg, respectively [54].

Safety and tolerability

Carvedilol and nebivolol have generally demonstrated a lower incidence of adverse events, including lower risks of adverse effects on lipid and carbohydrate metabolism, compared with conventional β-blockers; labetalol may also have more favorable metabolic effects, compared with conventional β-blockers, although supporting evidence is sparser for this agent [14,21,55–57]. In addition, β-blockers have long been associated with adverse effects on lipids and with an increased risk for new onset of diabetes, compared with other antihypertensive agents, except for diuretics, which pose an even greater risk [55,58].

Carvedilol

Carvedilol has been shown to improve the serum lipid profile of patients with dyslipidemia [14]. A study in patients with hypertension and impaired insulin sensitivity showed that although insulin sensitivity further declined by 14% with metoprolol, it increased modestly following carvedilol treatment [59]. In hypertensive patients with type 2 diabetes, fasting plasma glucose and insulin levels decreased with carvedilol and increased with atenolol [60]. Furthermore, the GEMINI trial in patients with hypertension and type 2 diabetes ($N = 1235$), who were also receiving an angiotensin-converting enzyme inhibitor or ARB therapy, showed that the addition of metoprolol was associated with significantly increased mean glycosylated hemoglobin A_{1c} (HbA_{1c}), whereas no change in HbA_{1c} occurred with carvedilol ($P = 0.004$ for the change in HbA_{1c} with carvedilol vs metoprolol); insulin resistance also was significantly reduced by carvedilol and increased by metoprolol ($P = 0.004$) (Fig. 3) [61••].

Nebivolol

In clinical studies, nebivolol has demonstrated an improved lipid profile in patients with dyslipidemia, and no adverse effects on lipids in patients with diabetes and hypertension [14]. Insulin sensitivity significantly decreased by about 20% with atenolol ($P < 0.01$) but remained unchanged with nebivolol in patients with hypertension and impaired glucose tolerance [62]. An insulin resistance index was also significantly reduced with nebivolol treatment, compared with metoprolol ($P = 0.003$), in hypertensive patients [46]. In other clinical trials, both atenolol and nebivolol had neutral effects on lipid or carbohydrate metabolism in normometabolic hypertensive patients [63], and nebivolol was associated with more favorable metabolic effects than atenolol in patients with hypertension and dyslipidemia, when pravastatin was added to both agents [64]. Nebivolol has also demonstrated neutral effects on carbohydrate metabolism and insulin sensitivity in patients with type 2 diabetes and hypertension [65].

Cardiovascular disease and outcomes

The β-blockers are well established as first-line therapies in patients with CV disease, including ischemic heart disease, post-MI, and HF [1,5]. The question remains whether vasodilating β-blockers will provide similar or different effects in these high-risk populations, based on their distinct hemodynamic profiles. Although labetalol has not been extensively studied in these populations,

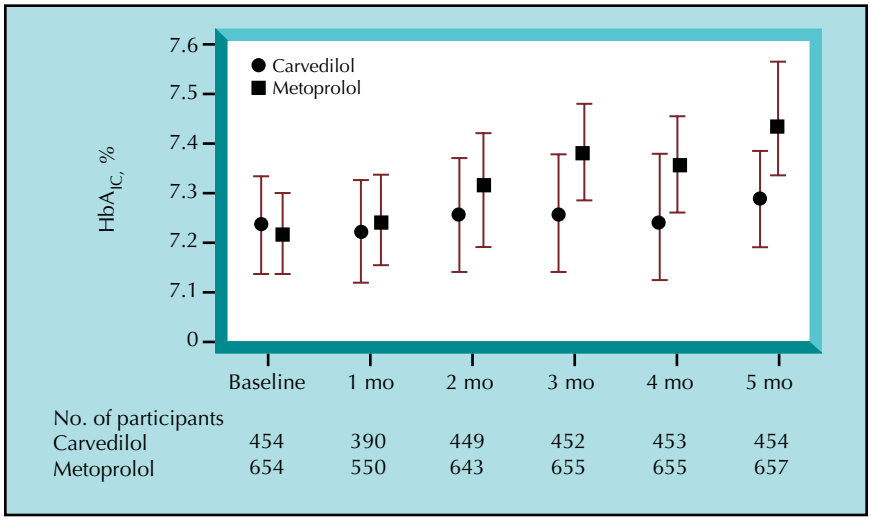

Figure 3. In the randomized double-blind GEMINI trial, hemoglobin A_{1c} (HbA_{1c}) increased significantly from baseline with metoprolol whereas no significant change occurred with carvedilol ($P = 0.004$, metoprolol vs carvedilol), in patients with hypertension and type 2 diabetes ($N = 1235$). (*Modified from* Bakris et al. [61••].)

some large-scale trials have been completed with carvedilol and nebivolol.

Carvedilol

In the CAPRICORN trial in patients with LV dysfunction following acute MI ($N = 1959$), carvedilol did not significantly reduce the primary composite endpoint of all-cause mortality and CV hospitalizations, but significantly reduced all-cause mortality by 23%, compared with placebo ($P = 0.03$) [66]. This result is within the range of risk reductions observed with other β-blockers in previous post-MI studies [67]. Carvedilol thus appears to be equally effective in post-MI patients as conventional β-blockers.

Carvedilol has significantly reduced morbidity and mortality in randomized controlled clinical trials in patients with chronic HF with reduced LV ejection fraction (LVEF) when added to standard therapy [68]. In the COPERNICUS study ($N = 2289$), carvedilol reduced overall mortality by 35% ($P = 0.0014$), compared with placebo, in patients with severe HF (LVEF < 25%), which is similar to the significant mortality risk reductions observed in large trials with metoprolol controlled-release or extended-release and bisoprolol in patients with moderate HF [68].

Nebivolol

The SENIORS trial was conducted to evaluate the effects of nebivolol on clinical outcomes in patients with chronic HF ($N = 2128$) who reflected the HF population in the general population, according to epidemiologic data [69•]. The previous large outcomes trials of β-blockers in HF were conducted in patients with systolic dysfunction and low LVEF, whereas many patients with chronic HF in the community, particularly older individuals, have only mildly reduced or preserved LVEF [69•]. Furthermore, the mean age in the previous β-blocker HF trials was 63 years, whereas the mean age of patients with HF in the general population is approximately 75 years [69•]. The SENIORS trial enrolled only patients 70 years of age or older with a diagnosis of HF regardless of LVEF; at baseline, the mean age of the study population was 76 years, and 35% of patients had LVEF greater than 35% [69•].

After a mean follow-up of 21 months, nebivolol had reduced the primary composite endpoint of all-cause mortality or CV hospital admission significantly by 14% ($P = 0.039$) and all-cause mortality by 12%; however, this reduction did not reach statistical significance. In a subgroup of patients comparable to those in previous β-blocker HF trials (patients younger than 75 years of age with LVEF ≤ 35%), nebivolol significantly reduced all-cause mortality by 38%, which is similar to the 35% mortality reductions observed with other β-blockers [69•].

Conclusions

Conventional nonvasodilating β-blockers (eg, atenolol) appear to provide less protection than other classes of antihypertensive agents against stroke and other CV outcomes, despite similar BP reduction. One possible explanation for this disparity is that atenolol is less effective at lowering central aortic pressure. However, vasodilating β-blockers (eg, carvedilol, labetalol, and nebivolol) may have different effects on CV outcomes because of different pharmacologic profiles and hemodynamic effects, compared with atenolol and other conventional β-blockers.

Vasodilating β-blockers generally reduce PVR and have neutral or beneficial effects on CO, stroke volume, and LV function, whereas conventional β-blockers increase PVR and reduce CO and stroke volume. In addition, vasodilating β-blockers have demonstrated significant antioxidant and antiproliferative actions, whereas conventional β-blockers usually show little or no such effects. Vasodilating β-blockers reduce BP to a similar degree as conventional β-blockers and other types of antihypertensive drugs, and are better tolerated than conventional β-blockers, particularly regarding effects on lipid and carbohydrate metabolism. Carvedilol significantly reduces outcomes in both post-MI patients and those with severe HF; nebivolol significantly reduces clinical outcomes in an elderly population with chronic HF regard-

less of LVEF. Although small trials have demonstrated that vasodilating β-blockers are more effective at lowering central pressure than atenolol, larger trials are needed to ascertain whether they will reduce the risk of clinical events compared with conventional nonvasodilating β-blockers.

Clinical Trial Acronyms

ASCOT-BPLA—Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm; CAFE—Conduit Artery Function Evaluation; CAPRICORN—Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; COPERNICUS—Carvedilol Prospective Randomized Cumulative Survival; GEMINI—Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives; SENIORS—Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure.

Acknowledgments

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- •• Of major importance

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