Commentary

β-Blockers in the Treatment of Hypertension: New Data, New Directions

Michael A. Weber, MD;[1] George L. Bakris, MD;[2] Thomas D. Giles, MD;[3] Franz H. Messerli, MD[4]

β-Blockers were first used for the treatment of hypertension in the early 1970s. The first clinically available member of this class, propranolol, which blocks both β_2 and β_1 receptors, was initially indicated for the treatment of angina pectoris and cardiac arrhythmias, and its efficacy as an antihypertensive agent was discovered later. There has never been a clear understanding of how β-blockade reduces blood pressure. Hemodynamically, these drugs decrease cardiac output; the slowing of heart rate was originally thought to be of clinical importance, particularly in hypertensive patients with tachycardia. But, at the same time, peripheral resistance is increased slightly and sodium reabsorption by the kidney is increased. The ability of β-blockers to inhibit activity of the renin-angiotensin system by reducing the release of renin from the juxtaglomerular cells of the kidney may contribute to their blood pressure–lowering effects, especially in patients with medium or high levels of plasma renin activity.[1]

One of the reasons for the acceptance of this new drug class by clinicians was that these agents appeared to be better tolerated than many of the drugs previously available for treating hypertension. Even so, β-blockers, at least in the dosages originally used, tended to decrease exercise tolerance and sexual activity levels and at times cause symptoms of fatigue and depression. The development of agents that selectively block the β_1 receptors, often referred to as cardioselective drugs, provided a relative measure of protection against adverse effects of β-blockade on airway function, particularly for patients with asthma and obstructive lung disease.

Over time, β-blockers became widely accepted for the treatment of hypertension, and 3 of the reports of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC)—JNC IV in 1988, JNC V in 1993, and JNC VI in 1997—recommended these drugs as one of the preferred medications for first-step treatment for the management of hypertension.[2–4] Recently, questions have begun to emerge about the ability of some β-blockers to provide as much protection against fatal and nonfatal cardiac and stroke events as other classes of antihypertensive drugs.

These concerns may appear surprising, as the β-blockers have been of unquestioned value in improving survival and reducing major cardiovascular events, particularly sudden death, in patients who have experienced myocardial infarction or heart failure.[5,6] Still, as emphasized in a recent commentary (coauthored by one of the writers of this editorial [FHM]), clinical trial evidence supports the conclusion that at least one of the widely used β-blockers should no longer be regarded as an appropriate choice for the routine treatment of uncomplicated hypertension.[7]

CONSIDERING THE EVIDENCE

Despite support for β-blockers in the guidelines' recommendations, scrutiny of the evidence that these agents provided clinical benefit, particularly in the elderly, began to raise serious concerns.[8]

From State University of New York, Downstate Medical College, Brooklyn, NY;[1] University of Chicago, Chicago, IL;[2] Tulane University, New Orleans, LA;[3] and St Luke's-Roosevelt Hospital, New York, NY[4]
Address for correspondence:
Michael A. Weber, MD, State University of New York, Downstate Medical College, 450 Clarkson Avenue, Brooklyn, NY 11023
E-mail: michaelwebermd@cs.com

www.lejacq.com ID: 7843

The Losartan Intervention for Endpoint Reduction (LIFE) study added to these questions. In high-risk patients with hypertension, the β-blocker atenolol was significantly more likely than the angiotensin receptor blocker losartan to be associated with stroke events in white patients but not in black patients.[9] Even earlier, British studies in elderly hypertensive patients had shown that β-blockers were inferior to thiazides in reducing morbidity and mortality; in fact, they were not significantly different from placebo.[10]

Not all the news was bad for the β-blockers, however. In another large British study testing the desirability of achieving tight blood pressure control in patients with type 2 diabetes mellitus, β-blocker–based therapy was at least equivalent to angiotensin-converting enzyme (ACE) inhibitor–based therapy in improving cardiovascular and diabetes-related outcomes.[11] In addition, a Scandinavian trial comparing differing drug classes for the management of hypertension in elderly patients demonstrated that event rates for patients receiving β-blockers, either alone or in combination with diuretics in two-thirds of patients, were similar to those for patients receiving other antihypertensive drugs.[12] In fact, in another subset of a Scandinavian study, admittedly one beset by methodologic issues, the β-blocker metoprolol appeared to be superior to a thiazide in preventing major coronary events in hypertensive men.[13]

Unfortunately, the preponderance of clinical outcomes data reviewed by meta-analyses across a broad range of clinical trials appears to be raising questions regarding the ability of β-blockers to protect against major hypertension-related clinical outcomes when compared with other antihypertensive drugs. β-Blockers—atenolol, most notably—appear to be associated with significantly higher rates of all-cause mortality, cardiovascular mortality, and especially stroke when compared with diuretics, ACE inhibitors, or calcium channel blockers (CCBs).[14] Even when compared with placebo, it appears that the outcome benefits of β-blocker therapy are relatively modest.[15] It is possible that some of the poor performance of atenolol might be related to using this relatively short-acting drug on a once-daily basis with inadequate doses.

A major cause for concern over the use of conventional β-blockers has come from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).[16] In this study, conducted in a large cohort of relatively high-risk middle-aged hypertensive patients, a comparison of atenolol-based treatment with a thiazide added if necessary vs a CCB-based regimen (amlodipine) with an ACE inhibitor (perindopril) added if necessary revealed that major cardiac and stroke outcomes favored the CCB/ACE inhibitor treatment arm. The ASCOT oversight safety committee recommended that the trial be terminated prematurely due to excess mortality in the patients randomized to the β-blocker arm. For many observers, these results suggested that treatment with a β-blocker–based regimen and a thiazide (which, at the time, were among the preferred antihypertensive agents recommended by guidelines committees) no longer represented appropriate therapy.

Explanations for this disappointing result are not entirely clear. It is well established, though, that the traditional β-blockers may produce adverse metabolic changes. Typically, they have unwanted effects on glucose and insulin metabolism and may even be diabetogenic.[17] The older agents also have adverse effects on the lipid profile: they decrease blood concentrations of high-density lipoprotein cholesterol and increase plasma triglyceride concentrations.[18] It is plausible that these β-blocker effects on glucose and lipid metabolism could at least partly explain the clinical outcomes differences between these agents and other drug classes.

A further tantalizing explanation for the fewer than expected benefits of β-blockers may lie with their hemodynamic effects. In a substudy of ASCOT, a noninvasive technique that estimates central (aortic) blood pressure as well as peripheral blood pressure was used to compare atenolol-based therapy with amlodipine-based therapy.[19] Interestingly, whereas the 2 treatment arms had similar blood pressure–lowering effects at the end of the trial when measured in the peripheral circulation, the β-blocker treatment was significantly less efficacious than the CCB treatment in reducing central pressure. This discovery provides an important insight, for it is likely that both cardiac and stroke events are particularly affected by the central blood pressure. As far as some β-blockers are concerned, this could provide a further explanation for their apparent failure to reduce major clinical events to the same extent as other therapies.

A NEW DIRECTION: THE VASODILATORY β-BLOCKERS

Two different β-blockers, carvedilol and labetalol, the so-called vasodilatory β-blockers, are already in wide use. Carvedilol is a nonselective β-blocker with additional α-blocking activity that has been available in the United States for several years. Nebivolol is a highly selective β_1-blocker with the

additional property of increasing the availability of vascular nitric oxide. Nebivolol, which is expected to be approved for use in the United States in early 2008, is already available in Europe and certain other countries. These vasodilating drugs have metabolic and hemodynamic properties that distinguish them from their predecessors in the β-blocker class.

Carvedilol is already widely used for the treatment of heart failure. It has been shown to prolong survival and reduce events in patients with chronic heart failure and also in patients who develop left ventricular systolic dysfunction following a myocardial infarction.[20] In a new long-acting formulation, carvedilol is an effective and well-tolerated once-daily antihypertensive agent.[21] Its additional α-blocking attributes probably explain its neutral or even slightly beneficial metabolic effects. In a large clinical trial conducted in hypertensive patients with type 2 diabetes already receiving blockers of the renin-angiotensin system, additional therapy with carvedilol was found to be as effective as treatment with metoprolol in reducing blood pressure.[22] However, the tendency toward adverse effects in glucose and lipid metabolism observed with metoprolol did not occur with the metabolically neutral carvedilol. It is possible, too, that the unique hemodynamic and metabolic properties of carvedilol might have an advantage in heart failure therapy: in a comparative trial with metoprolol, treatment with carvedilol was associated with better clinical outcomes as well as a reduced tendency to produce new-onset diabetes.[23]

The distinguishing feature of nebivolol is its ability to enhance the availability of nitric oxide. Nitric oxide mediates some of the key hemodynamic and vasoprotective properties of the vascular endothelium.[24] Compared with conventional β-blockers, and like carvedilol and labetalol, nebivolol has been shown to reduce peripheral resistance in hypertensive patients and to increase stroke volume.[25] This allows cardiac output to be maintained despite the modest decrease in heart rate associated with this drug's highly selective β-blocking properties. Nebivolol's hemodynamic profile is more similar to that of an ACE inhibitor or an angiotensin receptor blocker than other β-blockers without vasodilating properties. It is likely, too, that the vasodilatory properties of nebivolol help explain why, unlike most other β-blockers, its antihypertensive efficacy in black patients is equal to its efficacy in nonblacks.[26] Recent evidence indicates that nebivolol has a significantly greater effect on central blood pressure than atenolol.[27]

Carvedilol and nebivolol do not have the inhibitory effects on exercise tolerance that have previously been reported with β-blockers.[28] Both of these agents have been shown to have survival benefits in patients with heart failure, including patients who are elderly and have heart failure but preserved systolic function.[29] The metabolic effects of nebivolol are similar to those of carvedilol; for instance, using the euglycemic hyperinsulinemic clamp as well as other methods for measuring insulin sensitivity, this drug has been shown not to differ from placebo and to be superior to medications such as atenolol and metoprolol in maintaining glucose homeostasis.[30]

Of note, both vasodilating β-blockers, carvedilol and nebivolol, have lesser negative chronotropic effects than do traditional β-blockers. Recent data have shown that this may be an advantage in hypertensive patients receiving a β-blocker. In a recently reported meta-analysis of 34,096 patients receiving β-blockers, there was a negative correlation between heart rate and cardiovascular morbidity and mortality; slower heart rate was associated with greater all-cause mortality, cardiovascular mortality, stroke, and myocardial infarction.[31] This is in contrast to what other investigators have shown in the post–myocardial infarction population, in whom cardioprotection seems to be contingent on heart rate reduction.[32] Conceivably, vasodilating β-blockers used in hypertension may have an advantage over traditional agents in that they reduce heart rate less. This concept deserves further exploration.

LOOKING TO THE FUTURE

It is of interest to note how current published guidelines on hypertension management are addressing the β-blockers. JNC 7, which is now about 4 years old, lists β-blockers as possible initial drug therapy. In addition, this report appropriately emphasizes the importance of using β-blockers in patients who have a history of myocardial infarction or heart failure.[33] A recent meta-analysis based on intravascular ultrasonographic studies of the coronary circulation in patients with ischemic heart disease has concluded that β-blockers may actually be associated with regression of atheroma volume and so should be considered as treatments of choice in such patients.[34]

Following the disappointing performance of atenolol in ASCOT,[16] guidelines in Britain relegated β-blockers to third-line status for treating hypertension unless there are compelling reasons to use them sooner.[35] In contrast, the latest

edition of the guidelines of the European Society of Cardiology/European Society of Hypertension, after considerable evaluation of all available data, continues to include β-blockers among the other major drug classes as possible initial therapy.[36] Of note, however, these guidelines emphasize the positive attributes of the newer vasodilatory β-blockers, nebivolol and carvedilol, and recommend that they be the agents of choice due to their hemodynamic and metabolic features. Likewise, the American Association of Clinical Endocrinologists, while recommending that β-blockers be strongly considered as additive therapy in diabetic patients already receiving an ACE inhibitor or an angiotensin receptor blocker, indicate a preference for the vasodilatory agents.[37]

In many ways, β-blockers have demonstrated strong benefits in patients with a variety of cardiovascular conditions. Over time, evidence of symptomatic and metabolic adverse effects, together with concerns over major clinical outcomes, have led to some questioning of the use of older types of β-blockers for the routine treatment of hypertension, especially in elderly patients without heart disease. The emergence of the newer types of vasodilatory β-blockers should have the effect of reinvigorating interest in the β-blocker class.

Disclosures: Dr Weber is a member of the Speakers' Bureau of Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Forest Pharmaceuticals, GlaxoSmithKline, Merck, Novartis, Pfizer, and Sanofi-Aventis; he serves as a consultant for Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Forest Pharmaceuticals, Gilead, Merck, Novartis, and Takeda Pharmaceuticals. Dr Bakris has served as a consultant for and on the Speakers' Bureau/Advisory Boards of Abbott, Boehringer Ingelheim, Bristol-Myers Squibb/Sanofi-Aventis, Forest Pharmaceuticals, GlaxoSmithKline, Merck, Novartis, Walgreens (formulary committee), Gilead, and Daiichi Sankyo. He has received investigator-initiated grants from the National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases/National Heart, Lung, and Blood Institute), GlaxoSmithKline, and Forest Pharmaceuticals. Dr Giles is a member of the Speakers' Bureau of Boehringer Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, GlaxoSmithKline, Merck, Novartis, Pfizer, and Sanofi-Aventis; he serves as a consultant for Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Forest Pharmaceuticals, Merck, Novartis, and Takeda Pharmaceuticals. Dr Messerli has served as an ad hoc consultant/speaker for Abbott, GlaxoSmithKline, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Forest Pharmaceuticals, Daiichi Sankyo, Sanofi-Aventis, Merck, Jerini, Mars, and King Pharmaceuticals.

References

1 Buhler FR, Laragh JH, Baer L, et al. Propranolol inhibition of renin secretion: a specific approach to diagnosis and treatment of renin-dependent hypertensive disease. *N Engl J Med.* 1972;287:1209–1214.

2 The Fourth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC IV). *Arch Intern Med.* 1988;148:1023–1038.

3 The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med.* 1993;153:154–183.

4 Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med.* 1997;157:2413–2446.

5 Yusuf S, Peto R, Lewis J, et al. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis.* 1985;27:335–371.

6 Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure: a Bayesian meta-analysis. *Ann Intern Med.* 2001;134:550–560.

7 Bangalore S, Messerli FH, Kostis JB, et al. Cardiovascular protection using beta-blockers: a critical review of the evidence. *J Am Coll Cardiol.* 2007;50(7):563–572.

8 Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious aas first-line therapy for hypertension in the elderly? A systematic review. *JAMA.* 1998;279:1903–1907.

9 Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet.* 2002;359:995–1003.

10 MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ.* 1992;304:405–412.

11 UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ.* 1998;317:703–713.

12 Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet.* 1999;354:1751–1756.

13 Wikstrand J, Warnold I, Tuomilehto J, et al. Metoprolol versus thiazide diuretics in hypertension. Morbidity results from MAPHY Study. *Hypertension.* 1991;17:579–588.

14 Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet.* 2005;366:1545–1553.

15 Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA.* 2003;289:2534–2544.

16 Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet.* 2005;366:895–906.

17 Lithell HO. Effect of antihypertensive drugs on insulin, glucose, and lipid metabolism. *Diabetes Care.* 1991;14:203–209.

18 Rizos E, Bairaktari E, Kostoula A, et al. The combination of nebivolol plus pravastatin is associated with a more beneficial metabolic profile compared to that of atenolol plus pravastatin in hypertensive patients with dyslipidemia: a pilot study. *J Cardiovasc Pharmacol Ther.* 2003;8(2):127–134.

19 Williams B, Lacy PS, Thom SM, et al; CAFE Investigators; Anglo-Scandinavian Cardiac Outcomes Trial Investigators; CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation.* 2006;113:1213–1225.

20 Packer M, Fowler MB, Roecker EB, et al; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effects of carvedilol on morbidity of patients witih severe chronic heart failure: results of the carvedilol propective randomized cumulative survival (COPERNICUS) study. *Circulation.* 2002;106:2194–2199.

21 Weber MA, Bakris GL, Tarka EA, et al. Efficacy of a once-daily formulation of carvedilol for the treatment of hypertension. *J Clin Hypertens (Greenwich)*. 2006;8:840–849.

22 Bakris GL, Fonesca V, Katholi RE, et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA*. 2004;292:2227–2236.

23 Poole-Wilson PA, Swedberg K, Cleland JG, et al. Carvedilol or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomized controlled trial. *Lancet*. 2003;362:7–13.

24 Fratta Pasini A, Garbin U, Nava MC, et al. Nebivolol decreases oxidative stress in essential hypertensive patients and increases nitric oxide by reducing its oxidative inactivation. *J Hypertens*. 2005;23(3):589–596.

25 Kamp O, Sieswerda GT, Visser CA. Comparison of effects on systolic and diastolic left ventricular function of nebivolol versus atenolol in patients with uncomplicated essential hypertension. *Am J Cardiol*. 2003;92:344–348.

26 Saunders E, Smith WB, DeSalvo KB, et al. The efficacy and tolerability of nebivolol in hypertensive African American patients. *J Clin Hypertens (Greenwich)*. 2007;9(11):866–875.

27 Pedersen ME, Cockcroft JR. The vasodilatory beta-blockers. *Curr Hypertens Rep*. 2007;9(4):269–277.

28 Stoschitzky K, Stoschitzky G, Brussee H, et al. Comparing beta-blocking effects of bisoprolol, carvedilol and nebivolol. *Cardiology*. 2006;106(4):199–206.

29 Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26(3):215–225.

30 Celik T, Iyisoy A, Kursaklioglu H, et al. Comparative effects of nebivolol and metoprolol on oxidative stress, insulin resistance, plasma adiponectin and soluble P-selectin levels in hypertensive patients. *J Hypertens*. 2006;24(3):591–596.

31 Bangalore S, Sawhney S, Uretsky S, et al. Heart rate and antihypertensive therapy: Kjekshus hypothesis revisited [abstract]. Presented at: The American Heart Association Annual Meeting; November 3–7, 2007; Orlando, FL. AHA Scientific Sessions 2007 Presentations. 07-SS-A-13170-AHA.

32 Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. *Am J Cardiol*. 1986;57(12):43F–49F.

33 The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.

34 Sipahi I, Tuzcu EM, Wolski KE, et al. Beta-blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultrasonography trials. *Ann Intern Med*. 2007;147(1):10–18.

35 Sever P. New hypertension guidelines from the National Institute for Health and Clinical Excellence and the British Hypertension Society. *J Renin Angiotensin Aldosterone Syst*. 2006;7(2):61–63.

36 Mancia G, De Backer G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension: the Task force for the Management of Arterial Hypertension of the European society of Hypertension (ESH) and the European Society of Cardiology (ESC). *Eur Heart J*. 2007;28:1462–1536.

37 Hypertension AACE Task Force. American Association of clinical endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of hypertension. *Endocr Pract*. 2006;12(2):193.