The Changing Landscape of Hypertension and the Evolving Role of Vasodilatory Beta-Blockers

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

Jerome D. Cohen, MD, FACC, FACP, FAHA

Edgar R. Gonzalez, PharmD, FASHP, FASCP

Supplement

June 2007

Vol. 13, No. 5

Continuing Education Program

JMCP

Editor-in-Chief

Frederic R. Curtiss, PhD, RPh, CEBS
(830) 935-4319, fcurtiss@amcp.org

Managing Editor

Tamara C. Faggen, (703) 323-0170
tfaggen@amcp.org

Assistant Editor

Diane P. Britton
drbritton@verizon.net

Peer Review Administrator

Jennifer A. Booker, (703) 317-0725
jmcpreview@amcp.org

Graphic Designer

Elisabeth M. Squire, (703) 823-3159
ehsquire@comcast.net

June Supplement Editor

Brian J. Quilliam, PhD

Account Manager

Peter Palmer, (856) 795-5777, ext. 13
peter@promedgroup.net

Publisher

Judith A. Cahill, CEBS
Executive Director
Academy of Managed Care Pharmacy

This supplement to the Journal of Managed Care Pharmacy (ISSN 1083-4087) is a publication of the Academy of Managed Care Pharmacy, 100 North Pitt St., Suite 400, Alexandria, VA 22314; (703) 683-8416; (703) 683-8417 (fax).

Copyright© 2007, Academy of Managed Care Pharmacy.
All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, without written permission from the Academy of Managed Care Pharmacy.

POSTMASTER: Send address changes to JMCP, 100 North Pitt St., Suite 400, Alexandria, VA 22314.

FACULTY

George L. Bakris, MD, FACP, FAHA, FASN, is a professor of medicine and director, Hypertension Unit, Section of Endocrinology, Diabetes, and Metabolism, University of Chicago–Pritzker School of Medicine, Illinois. From 1988 to 1991 he served as director of renal research at the Ochsner Clinic and was a faculty member of Tulane University School of Medicine. He was also professor and vice chairman of preventive medicine and director of the Rush University Hypertension Center in Chicago from 1993 to 2006.

Bakris has published more than 300 articles and book chapters on kidney disease hypertension and progression of nephropathy. He is the editor or coeditor of 8 books, all dealing with kidney disease, diabetes, and the role of hypertension: *The Kidney and Hypertension*; *Hypertension: A Clinician's Guide to Diagnosis and Treatment*; *Hypertension: Principles and Practice*; *Handbook of Hypertension*; *The Kidney in Cardiovascular Disease*; *Therapeutic Strategies in Hypertension*; *Microalbuminuria and Cardiovascular Risk*; and *Lower Extremity Arterial Disease*. Additionally, he is the associate editor of the *International Textbook of Cardiology*. He has also served as the coprincipal investigator of a National Institutes of Health (NIH) clinical research training grant (1999-2004). He chaired the National Kidney Foundation Consensus Report on blood pressure and impact on renal disease progression (2000). He also served on many national committees, including the JNC 7 executive and writing committee (2003), the American Diabetes Association Clinical Practice Guideline Committee (2003-2004), the National Kidney Foundation (K-DOQI) Blood Pressure Guideline Committee (2002-2004), the National Kidney Foundation (K-DOQI) Diabetes Guideline Committee (2003-2005), the JNC 6 writing committee (1997), and the NIH National High Blood Pressure Education Program Working Group on Hypertension and Renal Disease (1994). He also serves as an expert consultant to the Cardio-renal Advisory Board of the U.S. Food and Drug Administration (1993-present).

Bakris is past president of the American College of Clinical Pharmacology (2000-2002). He is the current editor of the *American Journal of Nephrology* and is the hypertension section editor of *Up-to-Date*. He serves on more than 12 editorial boards, including *Diabetes Care*, *Kidney International*, *Nephrology*, *Dialysis & Transplant*, *Hypertension*, *Journal of Clinical Hypertension*, and *Journal of Hypertension*.

After receiving his medical degree from Chicago Medical School, Bakris completed a residency in internal medicine at the Mayo Graduate School of Medicine, where he also did a research fellowship in physiology and biophysics. He then completed fellowships in nephrology and clinical pharmacology at the University of Chicago.

Jerome D. Cohen, MD, FACC, FACP, FAHA, is director, Preventive Cardiology Programs, and a professor of internal medicine, Division of Cardiology, Saint Louis University School of Medicine, Missouri. He has been active in cardiovascular research for more than 3 decades. He has written more than 160 scientific articles and book chapters on heart disease with a primary focus on hypertension, dyslipidemias, and multiple-risk factors, including metabolic syndrome, diabetes, and the prevention of cardiovascular diseases. Cohen has served as a member of the executive committee for the Sixth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure, is a member of the MRFIT editorial committee, and was a recipient of the Preventive Cardiology Academic Award from the National Institutes of Health. He is a graduate of The Johns Hopkins University and Washington University School of Medicine.

Edgar R. Gonzalez, PharmD, FASHP, FASCP, is president and chief executive officer, Capital Pharmacy Consultants, Mechanicsville, Virginia. This multidisciplinary medical research and education corporation provides clinical pharmacy services, medical research, and education support to private hospitals, teaching institutions, and research foundations nationally. He established the University of Appalachia College of Pharmacy and served as its president and founding dean. Gonzalez also helped establish the Nevada College of Pharmacy, where he served as professor of pharmacy. He has served as associate professor of pharmacy at Hampton University and as associate professor of medicine and pharmacy at the Medical College of Virginia.

An avid researcher, Gonzalez is, to date, the only pharmacist to serve on the American Heart Association (AHA) National Advance Cardiac Life Support Committee. His research in the areas of human resuscitation and emergency cardiac care led to the implementation of the National Heart Attack Alert Program and the Practice Guidelines for the Treatment of Acute Cardiac Care by the National Institutes of Health and the AHA. He pioneered the use of patient-controlled analgesia in patients with sickle cell disease and vaso-occlusive pain crisis in the emergency department. Gonzalez founded the American Society of Health-System Pharmacists (ASHP) Specialty Practice Group for Critical Care Pharmacy, was its first chairman, and wrote ASHP Supplemental Standards and Learning Objectives for Residency Training in Critical Care Pharmacy. He served on the U.S. Pharmacopeia Critical Care Advisory Board from 1992 to 1998 and on the U.S. Food and Drug Administration's Advisory Committee for Pharmaceutical Sciences from 1994 to 1998. His dedication to geriatrics was recognized when he became the first recipient of the American Society of Consultant Pharmacists Foundation Fellowship Award in 1995. Most recently, Gonzalez has focused on the importance of treating anemia in patients with chronic kidney disease.

Also an avid author, Gonzalez has published more than 150 articles and 19 book chapters. His two textbooks, *Drug Therapy in Emergency Medicine* and *Field Drug Reference for Emergency Care Providers* are used by emergency medical service systems throughout the world. He is a reviewer for numerous scientific journals, research fellowship committees, and grant award committees.

Gonzalez received a bachelor of science degree in pharmacy from the Philadelphia College of Pharmacy and Science and a doctor of pharmacy degree and a graduate certificate in gerontology from the University of Utah. He completed a 2-year clinical pharmacy residency at the University of Utah Medical Center.

Supplement Policy Statement

Standards for Supplements to the *Journal of Managed Care Pharmacy*

Supplements to the *Journal of Managed Care Pharmacy* are intended to support medical education and research in areas of clinical practice, health care quality improvement, or efficient administration and delivery of health benefits. The following standards are applied to all JMCP supplements to assure quality and assist readers in evaluating potential bias and determining alternate explanations for findings and results.

1. Disclose the principal sources of funding in a manner that permits easy recognition by the reader.
2. Disclose the existence of all potential conflicts of interest among supplement contributors, including financial or personal bias.
3. Describe all drugs by generic name unless the use of the brand name is necessary to reduce the opportunity for confusion among readers.
4. Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.
5. Seek and publish content that does not duplicate content in the *Journal of Managed Care Pharmacy*.
6. Subject all supplements to expert peer review.

Table of Contents

The Changing Landscape of Hypertension and the Evolving Role of Vasodilatory Beta-Blockers

- S3** Current Perspectives on Hypertension and Metabolic Syndrome
George L. Bakris, MD, FACP, FAHA, FASN
- S6** Overview of Physiology, Vascular Biology, and Mechanisms of Hypertension
Jerome D. Cohen, MD, FACC, FACP, FAHA
- S9** Pharmacological Augmentation of Endothelium-Derived Nitric Oxide Synthesis
George L. Bakris, MD, FACP, FAHA, FASN
- S13** Case Study: Pearls in Hypertension Pharmacotherapy
Jerome D. Cohen, MD, FACC, FACP, FAHA
- S17** Case Study: The Link Between Hypertension and Diabetes
George L. Bakris, MD, FACP, FAHA, FASN, and Edgar R. Gonzalez, PharmD, FASHP, FASCP
- S20** Pharmacoeconomic Benefits of Antihypertensive Therapy
Edgar R. Gonzalez, PharmD, FASHP, FASCP
- S22** Continuing Education*:
CE Submission Instructions and Posttest Worksheet

Target Audience

Managed care pharmacists

Learning Objectives

Upon completion of this program, participants will be better able to

1. discuss current evidence regarding the epidemiology and pathophysiology of hypertension;
2. define metabolic syndrome and related cardiovascular consequences and recognize at-risk individuals;
3. state the effects of antihypertensive agents on endothelium-derived nitric oxide synthesis;
4. identify pharmacologic differences among beta-adrenergic blockers on beta-adrenergic selectivity, intrinsic sympathomimetic activity, vasodilatory effects, and safety parameters;
5. describe the impact of selected beta-adrenergic blockers on quality of life metrics and cost indicators in elderly patients and in those with diabetes, cardiovascular and renal diseases, and erectile dysfunction;
6. list target patient populations that would benefit from treatment with newer generation beta-blockers; and
7. evaluate the pharmacoeconomic impact of therapy with selected beta-blockers.

This supplement was funded by an educational grant from Forest Pharmaceuticals.

*A total of 0.20 CEUs (2.0 contact hours) will be awarded for successful completion of this continuing education program (ACPE Program No.788-000-07-001-H01). For faculty disclosures, please see pages S5, S8, S11, S16, S19, and S21. For accreditation information, please see page S22.

The articles published in this supplement represent the opinions of the authors and do not reflect the official policy or views of the Academy of Managed Care Pharmacy, the authors' institutions, or Forest Pharmaceuticals unless so specified. The authors have disclosed if any unlabeled use of products is mentioned in their articles. Before prescribing any medicine, clinicians should consult primary references and full prescribing information.

Current Perspectives on Hypertension and Metabolic Syndrome

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

ABSTRACT

BACKGROUND: Cardiovascular disease (CVD), which affects 79.4 million Americans, is a relentless problem that continues to grow by leaps and bounds.

OBJECTIVE: To review current perspectives on hypertension and metabolic syndrome.

SUMMARY: Hypertension can be considered a national burden: 1 in 3 American adults are hypertensive, lifetime risk of developing hypertension exceeds 90%, and the total direct costs related to hypertension and its complications approaches \$49.3 billion. The risk of CVDs doubles for every increment of 20/10 mm of mercury increase in blood pressure (BP), starting at 115/75 mm Hg. Untreated elevated systolic BP may galvanize artery stiffness, and coronary heart disease (CHD) risk rises as systolic BP rises. Thus, emphasis on diastolic pressure as a risk assessment tool can be misleading, particularly in advanced age.

CONCLUSION: Other risk factors for CHD include elevated cholesterol, low high-density lipoprotein cholesterol (HDL-C), smoking, and diabetes. The relative risk of cardiovascular death is increased in hypertensive patients with history of stroke, diabetes, and kidney disease. Finally, metabolic syndrome, consisting of obesity, low HDL-C, and elevated BP, triglycerides, and fasting glucose, affects 47 million people and increases diabetes and CVD risk.

KEYWORDS: Cardiovascular disease, Coronary heart disease, Hypertension, Cholesterol, Metabolic syndrome, Diabetes, Blood pressure

J Manag Care Pharm. 2007;13(5):S3-S5

Many Americans—79.4 million of them—are affected by 1 or more types of cardiovascular disease (CVD). Foremost among cardiac diagnoses is hypertension, affecting 72 million people. Approximately 79 million Americans have had myocardial infarctions (MIs). Coronary heart disease (CHD) affects 15.8 million people, and more than 5 million people have heart failure.¹ Clearly, CVD is a relentless problem that continues to grow by leaps and bounds.

With 1 in 3 American adults being hypertensive and with the lifetime risk of developing hypertension being greater than 90%, hypertension can be considered a national burden.¹ The risk of CVD doubles for every increment of 20/10 mm of mercury in blood pressure (BP), starting at 115/75 mm Hg.¹ This means that a BP as low as 135/85 mm Hg indicates increased risk. Most patients require 2 or more drugs to reach today's target BP of less than 140/90 mm Hg; those who have diabetes or kidney disease should strive for readings of less than 130/80.²

Estimates of expenditures related to hypertension and its complications in 2007 indicate that total direct costs will approach \$49.3 billion.¹ This expenditure's driving forces are medical durables, professional expenses, and hospital expenditures.

According to the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), BP is classified progressively from normal (120/80 mm Hg) to prehypertension (120-139 mm Hg systolic) to stages 1 and 2 hypertension (see Figure 1). This classification represents a change from previous reports in that prehypertension is a new designation. The term itself—prehypertension—was identified by patients as prompting them to take action. This classification also eliminates stages 3 and 4 hypertension; regardless of how high the BP rises, the strategy is the same once stage 2 is reached.³

FIGURE 1 JNC 7 Classification of Blood Pressure

NIH. NHLBI. JNC 7 Report 2004.²

DBP = diastolic blood pressure; JNC 7 = Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; SBP = systolic blood pressure.

Author

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

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

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.

Throughout life, systolic (but not usually diastolic) BP increases.⁴ In patients who have passed their 50th birthday, systolic blood pressure (SBP) is critical. Yet, many people at 70 are normotensive if only diastolic blood pressure (DBP) is examined.⁴

The prevalence of isolated systolic hypertension, isolated diastolic hypertension, and combined systolic/diastolic BP varies by age and gender data. Franklin et al. elucidated age-related changes in BP in normotensive and untreated hypertensive subjects using a population-based cohort (N=2,036) from the original Framingham Heart Study.³ After excluding subjects being actively treated for hypertension, they identified a linear rise in SBP from age 30 through 84 years and concurrent increases in DBP and mean arterial pressure. After age 50 to 60 years, DBP decline is consistent with increased large artery stiffness. Untreated elevated SBP may galvanize artery stiffness, creating a vicious cycle. This effect was observed independent of gender. The climb in systolic pressure was more dramatic in older females than in males. In fact, in hypertensive patients aged 65 to 89 years, elevated systolic hypertension predominates regardless of gender. Among patients aged 69 to 80 years, systolic hypertension represents 8% and 69% of all hypertension diagnosed in men and women, respectively.⁵ Thus, emphasis on diastolic pressure as a risk assessment tool can be misleading, particularly in advanced age.⁶

Multiple Risk Factors

The Multiple Risk Factor Intervention Trial (MRFIT) Research Group assessed the combined influence of BP, serum cholesterol level, and cigarette smoking on death from CHD, with a special emphasis on age. Using a large sample (N=316,099 men) who had been followed for 12 years, the group identified strong associations between SBP above 110 mm Hg and DBP above 70 mm Hg and mortality due to CHD, with SBP being a stronger predictor of death than DBP. Patients with BPs of 160/80 mm Hg were at the same risk as those with BPs of 160/100 mm Hg, indicating that a “normal” diastolic pressure was of little consequence. CHD risk rises as SBP rises.⁷

A concurrent diagnosis of diabetes compounds risk. Using data from MRFIT, Stamler et al. examined CVD mortality among 5,163 men who reported taking medication for diabetes.⁸ After 12 years, absolute risk of CVD death among diabetic men was 3 times higher than that of nondiabetic men regardless of age, ethnicity, and other risk factors. For a diabetic, cardiovascular mortality per 10,000 patient-years at any level of BP is a much higher risk than for somebody who is not diabetic.

Research has confirmed a “multiplier effect” for systolic pressure when several risky conditions are present. With kidney disease or end-stage renal disease, the relative risk approaches 2.8. Stroke incurs a relative risk of 2.7, and coronary disease increases relative risk 1.5 times.⁹⁻¹¹ So systolic pressure drives cardiovascular risk as gasoline fuels fire.

The 10-year risk for CHD is clearly associated with SBP and is further influenced by other risk factors: elevated cholesterol, low

FIGURE 2 Atherogenic Consequences of Metabolic Syndrome

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride.

high-density lipoprotein cholesterol (HDL-C), smoking, and diabetes. Clinicians must examine each individual's entire risk profile.¹²

Add Obesity to the Mix

Obesity is an issue unto itself, and metabolic syndrome is a growing concern. Obesity is now considered epidemic, and metabolic syndrome is an interplay of lipids, BP, and obesity. Forty-seven million people have metabolic syndrome. The diagnosis requires 3 or more of the following: obesity, low HDL-C, a BP in the pre-hypertensive range above 130/85 mm Hg, elevated triglycerides, and elevated fasting glucose.¹³ Metabolic syndrome increases diabetes and CVD risk. Mexican Americans have the highest age-adjusted prevalence (31.9%) of metabolic syndrome, followed by whites (23.8%) and African Americans (21.6%), who have similar incidences within their populations.²

Obesity is a real problem, wherein 5% of males aged 12 to 19 years have metabolic syndrome, doubling in prevalence to more than 10% in males aged 30 to 39 years and reaching 45% in males aged 60 to 69 years. Approximately one third of Americans between the ages of 50 and 59 years of both genders have metabolic syndrome.^{14,15} Figure 2 demonstrates how the atherogenic consequences of metabolic syndrome are blatant. Excessive weight causes insulin resistance (difficulty using insulin in the periphery for metabolism).

Insulin becomes elevated with obesity because higher insulin levels are necessary to send glucose into the cells. The beta cells in the pancreas become exhausted, increasing the risk of diabetes. Elevated serum fat content leads to dyslipidemia. The triad of hypertension, elevated lipids, and elevated risk for diabetes contributes to inflammation and accelerated risk of developing atherosclerosis.

DISCLOSURES

This article is based on a presentation funded by an educational grant from Forest Pharmaceuticals. The author discloses that he has received honoraria from Forest Pharmaceuticals for participation in this supplement. He discloses the following commercial/financial relationships through grant/research support, consultant services, speakers bureaus, and/or advisory boards: AstraZeneca, Abbott, Boehringer-Ingelheim, BMS/ Sanofi-Aventis, Kos, GlaxoSmithKline, Merck, Novartis, Lilly, Walgreens (Formulary Committee), NIH (NIDDK/NHLBI), and Atlas Foundation.

REFERENCES

1. American Heart Association and American Stroke Association. Heart disease and stroke statistics—2007 update. Available at: www.americanheart.org/downloadable/heart/1166712318459HS_StatsInsideText.pdf. Accessed March 16, 2007.
2. The National Institutes of Health and the National Heart, Lung and Blood Institute. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; 2004. Available at: www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf. Accessed March 17, 2007.
3. Franklin SS, Gustin W IV, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997;96:308-15.
4. Galarza CR, Alfie J, Waisman GD, et al. Diastolic pressure underestimates age-related hemodynamic impairment. *Hypertension*. 1997;30:809-16.
5. Kannel WB. Framingham study insights into hypertensive risk of cardiovascular disease. *Hypertens Res*. 1995;18:181-96.
6. Chobanian AV, Bakris GL, Black HR, et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-72.
7. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med*. 1992;152:56-64.
8. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434-44.
9. Kannel WB. Risk stratification in hypertension: new insights from the Framingham Study. *Am J Hypertens*. 2000;13(1 pt 2):3S-10S.
10. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. *N Engl J Med*. 1996;334:13-18.
11. Perry HM Jr, Miller JP, Fornoff JR, et al. Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension*. 1995;25(4 pt 1):587-94.
12. Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206-52.
13. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735-52.
14. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287:356-59.
15. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med*. 2003;157:821-27.

Overview of Physiology, Vascular Biology, and Mechanisms of Hypertension

Jerome D. Cohen, MD, FACC, FACP, FAHA

ABSTRACT

BACKGROUND: Our understanding of the process leading to hypertension is allowing us to adopt principles of therapy that may be more beneficial for patients.

OBJECTIVE: To review the physiology, vascular biology, and mechanisms of hypertension.

SUMMARY: Hypertension, particularly in high-risk patients, is a result of loss of balance and the absence of the ability to vasodilate normally. The interaction between the endothelial cell and the smooth muscle cell is very important in this process. The endothelium is a group of cells that produce compounds that are important in regulating vascular homeostasis by elaborating factors such as angiotensin II, nitric oxide (NO), endothelin, and prostaglandins. Specifically, NO is found in endothelial cells responsible for smooth muscle relaxation. Gaseous NO diffuses across the endothelial cell and into the underlying smooth muscle cell, where it stimulates the pathway of guanylate cyclase to produce vasorelaxation.

Normal endothelium maintains vascular tone and blood viscosity, prevents abnormal blood clotting and bleeding, limits inflammation of the vasculature, and suppresses smooth muscle cell proliferation. Abnormal endothelium causes increased inflammation and hypertrophy of the smooth muscle cells, promotes thrombosis and vasoconstriction, and creates a situation ripe for establishment and rapid growth of atherosclerotic plaques. Endothelial dysfunction also predicts poor outcome in patients with non-insulin-dependent diabetes mellitus and may worsen insulin resistance, increase vascular reactivity, and encourage macrovascular disease.

CONCLUSION: Understanding endothelial vasculature will be imperative as researchers develop newer compounds that may enhance NO formation within the vasculature.

KEYWORDS: Hypertension, Endothelium, Endothelial dysfunction, Nitric oxide, Nitric oxide synthases

J Manag Care Pharm. 2007;13(5):S6-S8

Our understanding of the process that leads to hypertension is allowing us to adopt principles of therapy that may be more beneficial for patients. When I was in medical school, we learned that the endothelium was a single cell lining that had a negligible role in the production of compounds affecting cardiovascular function—and that was wrong. Over the years, we have learned that the endothelium is a single layer of cells that surround the arteriole lumen. Underneath the endothelium are the smooth muscle cells. The interaction between the endothelial cell and the smooth muscle cell is very important. Underlying the endothelium and muscle is the third layer, the adventitia. The endothelium is a huge, living organ that has more cells than the liver, which is the largest organ in the body.

Our increased understanding of the endothelium's role began with the 1980 publication of Furchgott and Zawadzki's article with the obscure title, "The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine."¹ The first sentence in the abstract states, "Despite its very potent vasodilating action in vivo, acetylcholine does not always produce relaxation of isolated preparations of blood vessels in vitro." Furchgott and Zawadzki had observed that application of acetylcholine in vivo led to arterial vasodilatation. But in biological preparations of smooth muscle, the opposite occurred—vasoconstriction. They hypothesized that the endothelial cell had an important role in smooth muscle relaxation. In the absence of endothelial cells (the in vitro experiment), no vasodilatation occurred. Vasoconstriction did. This finding represented a considerable advance for medicine because the causative compound called endothelial-derived relaxing factor (EDRF) had yet to be identified and, in fact, remained unidentified for years. This work was eventually acknowledged with the Nobel Prize in physiology or Medicine in 1998.

Acknowledging Medical Breakthroughs

The 1998 Nobel Prize in physiology or medicine was jointly awarded to Robert Furchgott, Louis Ignarro, and Ferid Murad "for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system." Thus, EDRF was identified as nitric oxide (NO). The exact mechanism, shown in the figure, involves the endothelial cell and smooth muscle. Furchgott and Ignarro demonstrated that applying acetylcholine affects a muscarine receptor in the endothelial surface. It stimulates the enzyme NO synthetase to use L-arginine as a donor source for NO. Gaseous NO diffuses across the endothelial cell and into the underlying smooth muscle cell, where it stimulates the pathway of guanylate cyclase to produce vasorelaxation.

For years, physicians knew that NO—in a form that we use as nitroglycerin tablets sublingually—could help patients with angina or with chest pain due to ischemia. In actuality, giving NO sublingually bypasses the need for endothelial cell action and causes direct smooth muscle cell vasodilatation and symptom relief.

Author

JEROME D. COHEN, MD, FACC, FACP, FAHA, is director, Preventive Cardiology Programs, and a professor of internal medicine, Division of Cardiology, Saint Louis University School of Medicine, Missouri.

AUTHOR CORRESPONDENCE: Jerome D. Cohen, MD, 8138 Westmoreland Ave., St. Louis, MO 63105. Tel: (314) 721-2820; Fax: (314) 721-7976; E-mail: cohenjd@slu.edu

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.

FIGURE Physiology of Nitric Oxide (NO) in the Human Coronary and Peripheral Vasculature

Adapted from Quyyumi AA. *Am J Med.* 1998.

ACH=acetylcholine; cGMP=cyclic guanosine monophosphate;
GTP=guanosine 5'-triphosphate; L-NMMA=NG-monomethyl-L-arginine;
NOS=nitric oxide synthetase.

How does this apply to the endothelium? The endothelium is not a static cell but a group of cells that produce compounds that are important in regulating vascular homeostasis by elaborating factors such as angiotensin II, NO, endothelin, and prostaglandins. The net effect is maintenance of normal vascular tone. The endothelium also maintains normal blood viscosity, prevents abnormal blood clotting, and prevents abnormal bleeding in terms of a balance between plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator. It limits inflammation of the vasculature and it can suppress smooth muscle cell proliferation. These are functions of the normal endothelium. The opposite occurs in the presence of abnormal endothelium.

An abnormal endothelium creates a phenotype that presents in patients with coronary artery disease, diabetics, and high-risk patients. Abnormally functioning endothelial cells cause decreased NO formation and a decrease in vasodilatation, as well as decreased angiotensin I and prostaglandin formation. The net effect is increased inflammation and hypertrophy of the smooth muscle cells. An abnormal endothelium promotes thrombosis and vasoconstriction and creates a situation ripe for establishment and rapid growth of atherosclerotic plaques. The normal endothelium maintains vascular health by providing a balance between vasodilatation and vasoconstriction. Hypertension—particularly in high-risk patients—is a result of loss of balance and the absence of the ability to vasodilate normally.

Antihypertensives and Vasodilation

Panza et al. designed a study to determine whether using antihypertensive treatment in 15 controls and in 15 patients with essential hypertension restores impaired endothelium-dependent vasodilation.² They examined vascular responses to acetylcholine and sodium nitroprusside administered into the brachial artery in each patient: after withdrawal of medications, when the patients were hypertensive, and during the medical treatment that reduced BP to normal limits. Forearm blood flow response, a test of endothelial-dependent vasodilatation, was measured. In normotensive controls, acetylcholine-induced forearm blood flow increased with relatively modest reductions in vascular resistance. In the hypertensive patients, blood flow and vascular resistance responses to acetylcholine were significantly reduced. Responses to sodium nitroprusside, a direct vasodilator, were similar between groups. They concluded that clinically effective antihypertensive therapy does not restore the impaired endothelium-dependent vascular relaxation of patients with essential hypertension. Altered endothelial dysfunction is either primary or irreversible once the hypertensive process is established.

The importance of this finding was underscored by a study conducted by Murakami et al.³ Following 150 patients for 24 months, the researchers established lower, middle and upper tertiles of coronary blood flow increases in response to acetylcholine at the onset of the study. Patients who fell in the reduced endothelial function (lower) tertile experienced cardiac events at a higher rate than other tertiles. Fourteen percent experienced cardiac death, myocardial infarction, the need for revascularization, or worsening angina during the 24-month follow-up period. Two percent and 0% of patients in the middle and upper tertiles, respectively, experienced cardiac events. These findings are not only physiologically but prognostically important.

It remained to be determined whether NO-mediated vasodilation is abnormal in patients with non-insulin-dependent diabetes mellitus, which might explain the high prevalence of vascular disease in diabetes. Williams et al. looked at 21 patients with non-insulin-dependent diabetes mellitus and 23 matched healthy control subjects, again measuring vascular reactivity in the forearm resistance vessels.⁴ All study subjects were free of hypertension and hypercholesterolemia. The researchers pretreated subjects with aspirin to inhibit endogenous vasoactive prostanoid production, then administered methacholine chloride (an endogenous NO donor at 0.3 to 10 mcg/min) and sodium nitroprusside (an exogenous NO donor at 0.3 to 10 mcg/min). Although basal forearm blood flow in diabetic and nondiabetic subjects was comparable, forearm blood flow responses to methacholine chloride and nitroprusside were attenuated in diabetic subjects. The blunted response to exogenous as well as endogenous NO suggests either an increased NO inactivation or a decreased vascular smooth muscle reactivity. Again, endothelial dysfunction predicted poor outcome.

Using these findings, one can predict the interaction between insulin and the NO system. Again, acetylcholine using L-arginine

TABLE

Alterations in Vascular Endothelium Associated With Diabetes and Hypertension

Increased	Reduced	Impaired
Plasma levels of von Willebrand factor Expression, synthesis, and plasma levels of endothelin-1 Endothelial cell procoagulant activity Endothelial cell surface thrombomodulin Levels of advanced glycosylated end products	Prostacyclin release Release of endothelium-derived relaxing factor (NO) and responsiveness to NO	Fibrinolytic activity Plasmin degradation of glycosylated fibrin

Sowers JR, Epstein M. *Hypertension*. 1995.
NO = nitric oxide.

as a donor source and NO synthetase produce NO, which stimulates the smooth muscle guanylate cyclase. Vasodilation follows. Sodium nitroprusside or nitroglycerine, directly applied to smooth muscle cells, also causes vasodilatation.⁵

Insulin's Role

Insulin-mediated vasodilation in skeletal muscle appears to amplify insulin's ability to stimulate skeletal muscle glucose uptake in insulin-sensitive man. In insulin-resistant states (obesity, hypertension, and non-insulin-dependent diabetes mellitus), insulin-mediated vasodilation is blunted and endothelium-dependent vasodilation is impaired. Endothelial dysfunction is thus an integral aspect of insulin resistance, independent of hyperglycemia. It may worsen insulin resistance, increase vascular reactivity, and accelerate macrovascular disease. Insulin plays a key role in terms of healthy endothelium stimulating NO and smooth muscle cell vasodilatation.⁵

The table indicates exactly what changes one can expect to see in the diabetic or hypertensive person.⁶ All these atherogenic traits can cause problems in the high-risk patient. This demonstrates the importance of healthy endothelium in maintaining cardiovascular health and avoiding problems associated with abnormal endothelial function.

Summary

Nitroglycerine was first used as a vasodilator with no understanding of its mechanisms. Today its mechanisms have been elucidated, as have the links between hypertension and diabetes that are so common. Although many organizations have pushed to encourage physicians to control hypertension in the diabetic patient, we now see the link at the endothelial surface. We have moved forward from nitroglycerine to look at newer compounds that may use a NO synthetase mechanism to enhance NO formation within the vasculature. Understanding endothelial vasculature will be imperative as these new agents are developed.

DISCLOSURES

This article is based on a presentation funded by an educational grant from Forest Pharmaceuticals. The author discloses that he has received honoraria from Forest Pharmaceuticals for participation in this supplement. He discloses the following commercial/financial relationships through grant/research support, consultant services, speakers bureaus, and/or advisory boards: AstraZeneca, Sanofi-Aventis, King Pharmaceuticals, Novartis, and Merck.

REFERENCES

1. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature*. 1980;288:373-76.
2. Panza JA, Quyyumi AA, Callahan TS, Epstein SE. Effect of antihypertensive treatment on endothelium-dependent vascular relaxation in patients with essential hypertension. *J Am Coll Cardiol*. 1993;21:1145-51.
3. Murakami T, Mizuno S, Kaku B. Clinical morbidities in subjects with Doppler-evaluated endothelial dysfunction of coronary artery [abstract]. *J Am Coll Cardiol*. 1998;31:419A.
4. Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol*. 1996;27:567-74.
5. Baron AD. Insulin and the vasculature—old actors, new roles. *J Investig Med*. 1996;44:406-12.
6. Sowers JR, Epstein M. Diabetes mellitus and associated hypertension, vascular disease, and nephropathy. An update. *Hypertension*. 1995;26(6 pt 1): 869-79.

Pharmacological Augmentation of Endothelium-Derived Nitric Oxide Synthesis

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

ABSTRACT

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

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

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

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

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

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

J Manag Care Pharm. 2007;13(5):S9-S12

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

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

FIGURE

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

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

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

Author

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

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

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.

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

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

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

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

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

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

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

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

The Newest: Nebivolol

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

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

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

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

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

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

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

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

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

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

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

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

Summary

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

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

DISCLOSURES

This article is based on a presentation funded by an educational grant from Forest Pharmaceuticals. The author discloses that he has received honoraria from Forest Pharmaceuticals for participation in this supplement. He discloses the following commercial/financial relationships through grant/research support, consultant services, speakers bureaus, and/or advisory boards: AstraZeneca, Abbott, Boehringer-Ingelheim, BMS/ Sanofi-Aventis, Kos, GlaxoSmithKline, Merck, Novartis, Lilly, Walgreens (Formulary Committee), NIH (NIDDK/NHLBI), and Atlas Foundation.

REFERENCES

- Volpe M., Tocci G, Pagannone E. Fewer mega-trials and more clinically oriented studies in hypertension research? The case of blocking the renin-angiotensin-aldosterone system. *J Am Soc Nephrol.* 2006;17:S36-S43.
- Weber MA. The role of the new beta-blockers in treating cardiovascular disease. *Am J Hypertens.* 2005;18(12 pt 2):169S-176S.
- Braunwald E, Zipes DP, Libby P. *Heart Disease: A Textbook of Cardiovascular Medicine.* 6th ed. New York: WB Saunders Co.; 2001.
- Van de Water A, Janssens W, Van Neuten J, et al. Pharmacological and hemodynamic profile of nebivolol, a chemically novel, potent, and selective β_1 -adrenergic antagonist. *J Cardiovasc Pharmacol.* 1988;11:552-63.
- Bowman AJ, Chen CP, Ford GA. Nitric oxide mediated venodilator effects of nebivolol. *Br J Clin Pharmacol.* 1994;38:199-204.
- Van Nueten L, Taylor FR, Robertson JL. Nebivolol vs atenolol and placebo in essential hypertension: a double-blind randomised trial. *J Hum Hypertens.* 1998;12:135-40.
- Grassi G, Trevano FQ, Facchini A, Toutouzas T, Chanu B, Mancia G. Efficacy and tolerability profile of nebivolol vs atenolol in mild-to-moderate essential hypertension: results of a double-blind randomized multicentre trial. *Blood Press Suppl.* 2003;2:35-40.
- 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;92:344-48.
- Georgescu A, Pluteanu F, Flonta ML, Badila E, Dorobantu M, Popov D. The cellular mechanisms involved in the vasodilator effect of nebivolol on the renal artery. *Eur J Pharmacol.* 2005;508:159-66.
- Kalinowski L, Dobrucki LW, Szczepanska-Konkel M, et al. Third-generation beta-blockers stimulate nitric oxide release from endothelial cells through ATP efflux: a novel mechanism for antihypertensive action. *Circulation.* 2003;107:2747-52.
- Fortepiani LA, Ortiz MC, Atucha NM, Garcia-Estan J. Nebivolol ameliorates nitric oxide deficient hypertension. *Sci World J.* 2002;2:1676-84.
- Skarfors ET, Lithell HO, Selinus I, Aberg H. Do antihypertensive drugs precipitate diabetes in predisposed men? *BMJ.* 1989;298:1147-52.
- Samuelsson O, Hedner T, Berglund G, et al. Diabetes mellitus in treated hypertension: incidence, predictive factors and the impact of non-selective beta-blockers and thiazide diuretics during 15 years treatment of middle-aged hypertensive men in the Primary Prevention Trial Göteborg, Sweden. *J Human Hypertens.* 1994;8(4):257-63.
- Mykkanen L, Kuusisto J, Pyörälä K, et al. Increased risk of non-insulin-dependent diabetes mellitus in elderly hypertensive subjects. *J Hypertens.* 1994;12:1425-32.

15. Grimm RH. Antihypertensive therapy: taking lipids into consideration. *Am Heart J*. 1991;122:910-18.
16. Weber MA. Hypertension with concomitant conditions: the changing role of beta-adrenoreceptor blockade. *Am Heart J*. 1991;121:716-23.
17. Superko HR, Haskell WL, Krauss RM. Association of lipoprotein subclass distribution with use of selective and non-selective beta-blocker medications in patients with coronary heart disease. *Arteriosclerosis*. 1993;101:1-8.
18. von Fallois J, Faulhaber HD. Nebivolol, a beta blocker of the 3rd generation: modern therapy of arterial hypertension. Results of a multicenter observation study [article in German]. *Schweiz Rundsch Med Prax*. 2001;90:435-41.

Case Study: Pearls in Hypertension Pharmacotherapy

Jerome D. Cohen, MD, FACC, FACP, FAHA

ABSTRACT

BACKGROUND: Research and therapy only has relevance when applied to an actual patient.

OBJECTIVE: To review a case study of a patient with hypertension and diabetes.

SUMMARY: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) of 2004 recommends that a diagnostic workup include an assessment of risk factors and comorbidities using history, physical exam, and laboratory parameters. The presence of comorbidities influences drug selection. Patient evaluation should also include identification of possible causes of hypertension, such as renal arterial stenosis, and an assessment for the presence of target organ damage. Treatment is always influenced by the presence or absence of comorbidities. Lifestyle modifications are crucial to enhancing the success of pharmacologic therapy and should be ongoing. If lifestyle modifications do not work, the clinician must consider drugs. Study data and JNC 7 recommend beta-blockers for hypertension in patients with compelling indications, e.g., high risk for cardiovascular disease and diabetes.

CONCLUSION: JNC 7 emphasizes that evaluation for hypertension includes the assessment for the presence of compelling indications, e.g., diabetes, hyperlipidemia, and high coronary risk. These comorbidities may inform and direct pharmacologic choices.

KEYWORDS: JNC 7, Hypertension, Cholesterol, Diabetes, Blood pressure, Comorbidities, Lifestyle modification, Patient assessment

J Manag Care Pharm. 2007;13(5):S13-S16

Research and theory only has relevance when one is talking about an actual patient. This case study describes a 76-year-old Hispanic woman, RM, who has type 2 diabetes in addition to hypertension. She also has peripheral artery disease and lower extremity edema. Her chief complaint is her blood pressure (BP) and some associated fatigue. Her systolic blood pressure (SBP) ranges from 140 to 200 mm Hg and diastolic BP ranges from 70 to 104 mm Hg when measured at home. Our patient is 5'2" and weighs 175 pounds. Her body mass index (BMI) is 32 and her waist circumference is 36". She is afebrile with a pulse of 70. Her BP is elevated in the office at 160/84 mm Hg, even with repeated readings.

Her medications include the following:

- metoprolol XL 50 mg twice a day
- triamterene 37.5 mg/ HCTZ 25 mg once a day
- furosemide 40 mg once a day
- olmesartan 20 mg every bedtime
- metformin 1 gram twice a day
- clonidine 0.2 mg 4 times a day and as needed
- aspirin 81 mg once a day
- clopidogrel 75 mg once a day
- ezetimibe 10 mg/simvastatin 40 mg once a day

Despite these medications, her BP remains elevated.

During the past 4 weeks, her self-reported random blood glucose levels have ranged between 130 and 186 mg/dL. She adheres to her diet but indicates that glucose control became a problem when the metoprolol XL was added to the regimen. She also complains of bouts of headaches and some facial redness, both of which signal an acute rise in BP, for which she takes clonidine 0.2 mg 4 times a day and as necessary for relief.

■ Tailoring Care for the Hypertensive Patient

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) of 2004 recommends a diagnostic work-up beginning with an assessment of risk factors and comorbidities using history, physical exam, and laboratory parameters.¹ Comorbidities present influence the drugs available for this patient. We attempt to reveal identifiable causes of hypertension, such as renal arterial stenosis. We also assess for the presence of target organ damage, particularly examining the eye carefully for hypertensive retinopathy; review the EKG for the presence of left ventricular hypertrophy (LVH), which suggests hypertensive heart disease, and review laboratory tests (urinalysis, blood glucose, hematocrit and lipid panel, serum potassium, creatinine, calcium; optional: urinary albumin/creatinine ratio, an assessment for renal disease) and a 12-lead electrocardiogram.¹ Although JNC 7 indicates that the urinary albumin/creatinine ratio is considered optional, subsequent research has confirmed its importance in detecting early the presence of renal disease.

Author

JEROME D. COHEN, MD, FACC, FACP, FAHA, is director, Preventive Cardiology Programs, and a professor of internal medicine, Division of Cardiology, Saint Louis University School of Medicine, Missouri.

AUTHOR CORRESPONDENCE: Jerome D. Cohen, MD, 8138 Westmoreland Ave., St. Louis, MO 63105. Tel: (314) 721-2820; Fax: (314) 721-7976; E-mail: cohenjd@slu.edu

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.

In general, certain steps are essential when treating any patient with hypertension. Behavioral modification is often underemphasized. Weight loss with dietary restriction of simple carbohydrates and saturated fats is most important. In this diabetic patient, weight loss is critical because her glucose control is poor. Often, poor glucose control and poor BP control occur simultaneously. Weight loss is part of the standard treatment regimen and should be emphasized for every obese patient. Excess weight provides the underpinnings for metabolic syndrome: hypertension, dyslipidemia, and glucose intolerance or frank diabetes. It also indicates endothelial dysfunction.¹

Increased physical activity—as appropriate for the patient—is also critical. This 76-year-old woman could possibly increase her everyday physical activity by walking more and burning calories in other ways that are not arduous. This patient might be able to walk a few blocks or park the car a little farther away from a store on a nice day or walk down a flight of stairs rather than waiting for the elevator. Small energy expenditures in the form of brief exercise throughout the day over the long haul helps to control weight gain and can result in modest weight loss. Setting unattainable goals is an exercise in futility.¹

Many patients are better able to stabilize their BP if they maintain a normal BMI (18.5–24.9 kg/m²). Clinical trials have looked at the effect of weight loss on BP reduction. With each weight loss of 22 pounds (10 kilograms), SBP drops 5 to 20 mm Hg. Despite this significant improvement, the difficult, frustrating nature of weight loss sometimes discourages physicians and other health care providers from even recommending it.¹

In terms of diet, the Dietary Approaches to Stop Hypertension (DASH) eating plan is a diet rich in fruits and vegetables enriched with low-fat dairy products as a source of calcium. This diet reduces total saturated fat. Adhering to the DASH program has resulted in SBP reductions in the range of 8 to 14 mm Hg. Recommending dietary sodium reduction is important for all hypertensive patients, even though most people will respond, “I don’t eat salt, I don’t add it at the table, and I don’t cook with it.” Heightening their awareness that 70% of the sodium we consume is derived from processed foods and teaching them how to read labels will help, as will directing them to low-sodium products available as alternatives for most foods. Sodium reduction can lower BP an additional 2 to 8 mm Hg above that achieved with weight loss.¹

Alcohol restriction or reduction is important for those who have a more than moderate intake (2 drinks per day for men, 1 per day for woman). When taken to excess, alcohol can contribute to high BP and is also associated with poor adherence to medical regimens.¹

Basically, the goal is a stable, consistent foundation of a prudent lifestyle consuming fewer calories, increasing physical activities when possible, and making good lifestyle choices. The particular patient in this case study is high risk, having hypertension, diabetes, and dyslipidemia. Appropriate lifestyle modification can address all 3 problems.

Selecting Appropriate Pharmacotherapy

Treatment is always influenced by the presence or absence of comorbidities. If lifestyle modifications do not work, the clinician must consider drugs. The figure demonstrates the steps the clinician would consider for active drug treatment, according to JNC 7.¹

JNC 7 stages hypertension, and an SBP of 140 to 159 mm Hg is considered stage 1 hypertension; JNC 7 recommends monotherapy initially. A thiazide, angiotensin-converting enzyme inhibitor (ACEI), beta-blocker, calcium channel blocker (CCB), or a combination, if necessary, is appropriate as a first step. In an uncomplicated patient, the goal is usually less than 140 mm Hg systolic and less than 90 mm Hg diastolic. Generally, the lower the pressure, the better; there is nothing magical about 139/89 mm Hg. Using lifestyle intervention with drug therapy can help move the BP reading more toward an optimal reading.¹

Patients with stage 2 hypertension (SBP >160 mm Hg) may require treatment with 2 drugs, even initially. Usually, a thiazide is included in 2 drug regimens because it works well in combination with other antihypertensives, including beta-blockers, angiotensin II receptor blockers (ARBs), and ACEIs or CCBs. Clinical judgment is important, as is awareness of comorbid conditions.

Patients who have *compelling indications* for specific drug classes are handled differently. Compelling indications are those indications in which benefit from a specific agent has already been shown. An example is beta-blockers’ association with a reduction in myocardial infarction (MI). Clinicians choose a beta-blocker for patients with histories of MI to capitalize on its ability to reduce the likelihood of recurrent MI and to lower BP.

If the patient’s BP does not reach the goal, we will perhaps increase the dose (if it is not already at the maximum recommended dose) and/or add another agent.

A meta-analysis of trials (N=18,883) investigating the use of beta-blockers in hypertension was conducted in 1997. Beta-blockers

were associated with a reduction in cardiovascular disease (CVD). Psaty et al. identified a significant reduction in heart-failure (42%) and stroke (29%) and a less robust reduction in coronary events (7%), which was not quite statistically significant. These findings make sense because stroke and heart failure are closely correlated to hypertension. The correlation coefficient of BP to heart failure and stroke is much greater than the correlation coefficient with coronary disease.²

Beta-blockers are used less in hypertensive patients with diabetes, kidney disease, or stroke. Total beta-blocker use in hypertension with heart failure is 56%, which reflects a need for increased understanding by physicians of the importance of these agents. Part of the problem rests with the historical contraindication of beta-blocker use in patients with heart failure. This contraindication has been put to rest, and we know that reducing the sympathetic responsiveness in heart failure can reduce adverse cardiac events. Three quarters of prescribers use beta-blockers as an intervention for compelling indications in the post-MI patient. In patients with high risk for CVD who do not have heart failure or have had an MI, the use of beta-blockers lags at 37%.³

Clinical trials and guidelines for compelling indications for individual drug classes indicate when diuretics, beta-blockers, ACEIs, ARBs, CCBs, and aldosterone antagonists should be employed. For beta-blockers, the best candidates are heart-failure patients (in whom beta-blockers are, in fact, a standard of care); post-MI patients to reduce the likelihood of recurrent MI; high-risk coronary patients to improve endothelial function; and in highest-risk patients (diabetics).¹

Regulatory agencies have approved beta-blockers for a remarkable number of indications, but beta-blockers can be differentiated on the basis of beta₁ selectivity, duration of action, intrinsic sympathomimetic activity, lipophilicity, and whether the beta-adrenergic blocking action is accompanied by an alpha-adrenergic blocking action. Nebivolol's ability to activate nitric oxide (NO) synthetase in blood vessels is a unique therapeutic option. It may be useful in a range of off-label indications.⁴ Its utility in high-risk patients appears to be quite broad. Heart failure, prolonged QT interval syndrome (a common cause of sudden death), and myopathies are just a few possible conditions where it may be useful; however, it must be emphasized that these are not approved indications.⁴

Primary care physicians' perception of antihypertensives' effectiveness can be seen in their prescription choices. For physicians who tend to prescribe ACEIs or CCBs first, these therapies are perceived to be effective in 62% and 58% of patients, respectively. For beta-blocker and diuretic therapies, the physicians' perceived effectiveness was 55% and 39%, or about the same as for those physicians who did not prescribe these agents first. This is not a statistically significant difference. Evaluating the *P* values for beta-blockers (*P*=0.46) and for diuretics (*P*=0.12) shows that because the ACEI and CCB difference is statistically significant for perceptions by physicians playing a role in their initial choice of

TABLE Perceived Effectiveness of Antihypertensives by PCPs by Prescription Choice⁵

	Physicians Prescribing ACEI or CCB (N = 190)*	Physicians Prescribing BB or Diuretic (N = 176)*	P Value Comparison Between Physician Group
Effectiveness [Mean (SD) % of time drug expected to be effective]			
ACEI	62 (23)	49 (27)	<0.001
BB	53 (26)	55 (24)	0.46
CCB	58 (24)	51 (27)	0.006
Diuretic	35 (23)	39 (26)	0.12

* N = total of effectiveness and tolerability data.

ACEI = angiotensin-converting enzyme inhibitor; BB = beta blocker; CCB = calcium channel blocker; PCP = primary care physician.

therapy, the effectiveness of the drugs eventually influences their decision regardless of what they believe initially. If a physician really believes something is going to work, he or she will use it. Through education, physicians will understand that older drugs, like beta-blockers and diuretics, still have an important role in treating hypertension. Newer agents, and particularly the beta-blocking agents, actually can improve endothelial function and should be considered; that opportunity wasn't available in the past (Table).⁵

JNC 7 emphasizes that evaluation for hypertension includes assessing for the presence of compelling indications; e.g., diabetes, hyperlipidemia, and high coronary risk. These comorbidities may determine specific pharmacologic choices. Lifestyle modifications are crucial to enhancing the success of pharmacologic therapy and should be ongoing. Study data and JNC 7 recommend beta-blockers for hypertension in patients with compelling indications; e.g., at high risk for CVD and diabetes.

Edgar R. Gonzalez, PharmD, served as moderator for this program (see Faculty).

Dr. Gonzalez: Many years ago, the JNC promoted the statement, "Let's go with step care." Step care promulgated diuretics as first-line treatment, beta-blockers as second line, and newer agents as third line. Then, a later version of JNC proposed making step care less rigid. Are we seeing a rebirth of beta-blockers? And why has step care been deemphasized?

Dr. Cohen: Step care was based on Veterans Administration [VA] studies that demonstrated the benefit of lowering blood pressure. The VA started with a diuretic and added reserpine if necessary. Beta-blockers were not available. Hydralazine was used as a vasodilator, and guanethidine was the fourth-step drug. All these drugs have, for the most part, outlived their utility. Applying the VA algorithm for uncontrolled hypertension was the standard for 10 to 12 years. Many physicians labeled it "cookbook medicine" and did not use step care.

Medicine's advances brought new pharmacologic agents: beta-blockers, CCBs, ACEIs, and most recently, ARBs. This expanded armamentarium and the clinical trials provided the basis for making specific recommendations with respect to compelling indications. JNC guidelines, using the evidence available, evolved. For some patients, nonpharmacologic treatment is appropriate and effective. Allowing an element of clinical judgment persuaded many physicians to conduct careful history, physical, and laboratory assessments to determine which drug to use.

Current medical practice incorporating evidence-based treatment guidelines indicates that patients are being treated more appropriately and control of hypertension is better overall. We now understand that lowering SBP below 140 mm Hg is better, but we are not necessarily satisfied with a target of 139 mm Hg. In the diabetic patient, for example, and now the renal patient, we understand that we should have an often difficult-to-achieve goal of less than 130 mm Hg. Some of the older drugs, namely, diuretics and beta-blockers and particularly the third-generation beta-blockers, have a lot to offer in terms of maximizing blood pressure reductions and providing benefits beyond just the blood pressure lowering.

Dr. Gonzalez: *You were involved with JNC 7 and you have a great understanding of the Multiple Risk Factor Intervention Trial. Is it fair to say that MRFIT opened our eyes to the fact that blood pressure is just not a value or an independent number?*

Dr. Cohen: That's true. Medical professionals now see the continuous relationship between blood pressure and risk for heart attack, stroke, and heart failure. An SBP of 100 plus the patient's age used to be considered acceptable. The MRFIT and Systolic Hypertension in the Elderly Program [SHEP] studies using diuretics and beta-blockers demonstrated that prudent drug use could contribute to a significant reduction in morbidity and mortality.⁶⁻⁸ Subsequently, heart failure admissions to hospitals, the number 1 diagnosis-related group in this country for Medicare patients, fell 54%, strokes were reduced by 33%, and heart attacks fell approximately 20%.⁹

Higher BP over time is not something we should write off to old age. It is a treatment target because the risk of stroke, heart attack, and heart failure is real. Patients fear strokes. This fear often persuades them to take medications and may improve adherence.

Dr. Gonzalez: *You've served on JNC 7 and have brought us up-to-date on the knowledge of NO synthetase. Why have the British downplayed beta-blockers in their National Institute for Health and Clinical Excellence (NICE) guidelines?*

Dr. Cohen: The British scientists, using a study they conducted called Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), found that the blood-pressure-lowering arm that used a CCB and an ACEI versus a beta-blocker (atenolol) and a diuretic did better.¹⁰ But the data show that, in compelling indications populations, beta-blockers are the drugs of choice for the high-risk patient. Vasodilating ability can not only lower blood pressure but can also improve endothelial function and thereby reduce morbidity and mortality. Beta-blockers are an important class of drugs to use

or consider using in the hypertensive patient with comorbidities and in those patients who are at high risk.

Dr. Gonzalez: *In essence, the data from the Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensives [GEMINI] trial and some newer studies show that not all beta-blockers are created equal; some third-generation beta-blockers may not mimic what atenolol did in the ASCOT trial. In the future, we may increase our dependency on beta-blockers in hypertension in the patient with multiple risk factors.*

Dr. Cohen: Yes, the ASCOT study used atenolol, but in the post-MI studies, atenolol was never used. Those studies used propranolol, metoprolol, and timolol. Timolol is now used predominantly in ophthalmic preparations. Atenolol is short acting and has not been studied for MI, and that is why we do not use it. We often discuss actions and effects of beta-blockers and call them class effects. The second- and third-generation drugs have demonstrated that it's anything but a class effect. Specific agents have specific and unique actions.

DISCLOSURES

This article is based on a presentation funded by an educational grant from Forest Pharmaceuticals. The author discloses that he has received honoraria from Forest Pharmaceuticals for participation in this supplement. He discloses the following commercial/financial relationships through grant/research support, consultant services, speakers bureaus, and/or advisory boards: AstraZeneca, Sanofi-Aventis, King Pharmaceuticals, Novartis, and Merck.

REFERENCES

1. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-72.
2. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA*. 1997;277:739-45.
3. Market Measures, The Treatment of Hypertension Study XXVI, Analytical Report 2004.
4. Hollenberg NK. The role of beta-blockers as a cornerstone of cardiovascular therapy. *Am J Hypertens*. 2005;18(12 pt 2):165S-168S.
5. Ubell PA, Jepson C, Asch DA. Misperceptions about beta-blockers and diuretics: a national survey of primary care physicians. *J Gen Intern Med*. 2003;18:977-83.
6. Cutler JA, Neaton JD, Hulley SB, Kuller L, Paul O, Stamler J. Coronary heart disease and all-causes mortality in the Multiple Risk Factor Intervention Trial: subgroup findings and comparisons with other trials. *Prev Med*. 1995;14:293-311.
7. Kostis JB, Davis BR, Cytlar J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. *JAMA*. 1997;278:212-16.
8. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA*. 1991;265:3255-64.
9. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Prospective Studies Collaboration. *Lancet*. 2002;360:1903-13.
10. Dalhof 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(9489):895-906.

Case Study: The Link Between Hypertension and Diabetes

George L. Bakris, MD, FACP, FAHA, FASN, and Edgar R. Gonzalez, PharmD, FASHP, FASCP

ABSTRACT

BACKGROUND: Many diabetics develop hypertension, and it is a major risk factor for cardiovascular and microvascular complications.

OBJECTIVE: To review a case study of a patient with poorly controlled hypertension and diabetes.

SUMMARY: Further assessment of this case study shows that the patient has poorly controlled hypertension, despite multiple medications. The patient also has metabolic syndrome complicated by diabetes, microalbuminuria and peripheral arterial disease. The patient's hypertensive treatment options must be evaluated in light of the fact that polypharmacy has made it more difficult for her to achieve glycemic control. A panoply of drugs and drug classes are available from which to choose: diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone antagonists. New vasodilatory beta-blockers reduce adverse drug reactions and produce beneficial effects on arterial vasculature. Various beta-blockers' effects on insulin sensitivity are compared.

CONCLUSION: Older beta-blockers have been shown to have detrimental effects on glucose or lipid parameters. Newer agents such as nebivolol do not impact lipid, glucose, insulin, or high-density lipoproteins. Instead, nebivolol stimulates endothelial nitric oxide release in renal arteries and improves renal function.

KEYWORDS: Hypertension, Diabetes, Beta-Blockers, Nebivolol, Third-generation beta-blockers, Patient assessment

J Manag Care Pharm. 2007;13(5):S17-S19

Many diabetics develop hypertension. It is a major risk factor for cardiovascular and microvascular complications and often results from nephropathy in type 1 diabetes. Hypertension may be present as part of metabolic syndrome (i.e., obesity, hyperglycemia, and dyslipidemia), which contributes to high rates of cardiovascular disease in type 2 diabetics. Clinical trials confirm that lowering blood pressure (BP) to less than 140/80 mm Hg in diabetic patients reduces cardiac events, stroke, and nephropathy. When treating hypertension in diabetics, clinicians target a lower BP—130/80 mm Hg—in an attempt to reduce the likelihood of cardiac events and stroke.¹

For many years, clinicians believed beta-blockade should be avoided in diabetics. A 1990 study published in the *European Heart Journal* compared diabetic patients with nondiabetic patients to determine the effect of beta-blocker therapy following acute myocardial infarction (MI). Their large multicenter cohort (N=2,024) included 340 diabetics, 281 of whom survived hospitalization. One year later, the mortality rate was 10% for nondiabetics, and 7% and 13% for those taking and not taking beta-blockers, respectively. For diabetics overall, mortality was 17%, but diabetics discharged on beta-blockers had a mortality of 10%, compared with 23% for diabetics not on beta-blockers. In diabetics, pulmonary congestion was more prevalent than in nondiabetics, regardless of whether they were taking beta-blockers. Beta-blocker use independently predicted 1-year cardiac survival following hospital discharge for all diabetics. These data began to highlight the importance of using beta-blockade among diabetic patients after acute MI.²

In this case study, assessment shows that patient RM has poorly controlled hypertension, despite multiple medications. RM has metabolic syndrome complicated by diabetes, microalbuminuria, and peripheral artery disease. Her antihypertensive treatment options must be evaluated in light of the fact that RM has complained that the addition of metoprolol XL made it more difficult for her to achieve glycemic control.

A panoply of drugs and drug classes are available from which to choose: diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone antagonists account for more than 130 antihypertensive medications. The new beta-blockers must fit into this crowded field. Traditional beta-blockers, while reducing cardiovascular events, may have unwanted metabolic effects. New vasodilatory beta-blockers reduce adverse drug reactions and produce beneficial effects on arterial vasculature. Carvedilol has alpha-blocking actions; nebivolol stimulates nitric oxide (NO). These new agents may be especially useful in heart failure; carvedilol is indicated for both acute and chronic heart failure.³

The double-blind, randomized Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensives

Authors

GEORGE L. BAKRIS, MD, FACP, FAHA, FASN, is a professor of medicine and director, Hypertension Unit, Section of Endocrinology, Diabetes, and Metabolism, University of Chicago-Pritzker School of Medicine, Illinois.; EDGAR R. GONZALEZ, PharmD, FASHP, FASCP, is president, Capital Pharmacy Consultants, Mechanicsville, Virginia.

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

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.

(GEMINI) trial⁴ looked at carvedilol's possible metabolic effects, comparing it with immediate-release metoprolol tartrate. Both drugs were administered twice daily to 1,235 patients with hypertension and type 2 diabetics receiving an ACEI or an ARB. Thus, renin angiotensin system inhibition was ubiquitous. Study subjects' BPs were in the prehypertensive to hypertensive range, and glycosylated hemoglobins (A1Cs) were between 6.5% and 8.5%. Metoprolol doses were initiated at 50 mg and carvedilol was administered at 6.25 mg, each twice daily. Both drugs were titrated up as necessary; the mean daily dose of metoprolol was 256 mg and carvedilol was 35 mg. The trial's primary endpoint was the difference in the change from baseline in A1C at 5 months. Although both groups' BPs were similar, mean A1C increased with metoprolol, but not with carvedilol. Carvedilol-treated patients also had improved insulin sensitivity, but metoprolol-treated patients did not, with more than two thirds of study subjects achieving a BP of $\leq 130/80$ mm Hg. Progression to microalbuminuria was less frequent with carvedilol than with metoprolol.

Beta-blockers are used less in hypertensive patients with diabetes, kidney disease, and stroke. Older beta-blockers like atenolol and metoprolol have been shown to have detrimental effects on glucose or lipid parameters. Nebivolol does not affect lipid, glucose, insulin, or high-density lipoprotein cholesterol (HDL-C). It stimulates endothelial NO release in renal arteries and improves renal function.

Metabolic Effects of Beta-Blockers

The figure compares various beta-blockers' effects on insulin sensitivity. Celiprolol, carvedilol, and dilevalol all improve insulin sensitivity. The traditional, vasoconstricting beta-blockers do not.⁵

FIGURE Impact of Beta-Blockers on Insulin Sensitivity in Patients With Hypertension

Jacob S, Rett K, Henriksen EJ. *Am J Hypertens*. 1998.⁵

Triglyceride elevation and low-density lipoprotein cholesterol elevations do occur with propranolol, atenolol, and metoprolol.⁶ A study by Rizos et al. conducted in Europe and published in 2003 compared 2 beta-blockers (nebivolol and atenolol) in combination with a statin (pravastatin) to determine if interference with lipid metabolism differed.⁶ Thirty hyperlipidemic patients with concurrent hypertension were treated with either atenolol 50 mg daily (n=15), or nebivolol therapy 5 mg daily (n=15). After 12 weeks of therapy, each group added pravastatin 40 mg daily. Atenolol increased triglyceride levels by 19%; nebivolol increased HDL-C by 8% and decreased triglyceride levels by 5%, but these findings were not significant. Triglycerides kill the beta-cells in the pancreas and are thus important.

Fibrinogen levels were equally and not significantly decreased in both groups by 9% and 7%, respectively. Serum high-sensitivity C-reactive protein levels also fell in atenolol patients by 14% and in nebivolol patients by 15%. In the nebivolol group, glucose levels remained the same, while insulin levels were reduced by 10% and the homeostasis model assessment index (a model of insulin sensitivity calculated using fasting glucose levels multiplied by fasting insulin levels and divided by 22.5) was reduced by 20%. Measures of inflammation, homocysteine levels, and C-reactive protein fell 17% and 43%, respectively.⁷

Pooled analysis of 3 pivotal trials looked at the effects of nebivolol on glucose and lipid levels. At the probable maximum dose of 10 mg, no significant change in triglycerides was found.⁸

Other Effects of Nebivolol

Researchers have looked at many of the other effects of nebivolol compared with older beta-blockers, often using animal studies. They have found the following:

- Several beta-blockers, including nebivolol, exert their vasodilatory action through the 5-HT_{1A} receptor/NO pathway and that treatment with these beta-blockers may protect against renal endothelial injury in hypertension.
- With respect to renal plasma flow, in the presence of a NO blocker, vasodilation does not occur. But in its absence, renal blood flow increases.⁹

Erectile dysfunction (ED) is a serious concern and can affect adherence to medications. In a recent study, 44 men aged 31 to 65 years with essential hypertension received atenolol, metoprolol, or bisoprolol for 6 months or more. Results of the International Index for Erectile Function questionnaire revealed that 65.9% experienced beta-blocker-induced ED. After switching to an equipotent dose of nebivolol for 3 months, 11 of the 44 (65.9%) reported their erectile function had normalized. This outcome may be due to increased NO availability.¹⁰

Use of beta-blockers in the elderly also raises special concerns, especially with regard to left ventricular function. Numerous trials (the U.S. Carvedilol Trials,¹¹ Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure [MERIT-HF],¹² Cardiac Insufficiency Bisoprolol Study [CIBIS],¹³ and Carvedilol Prospective

Randomized Cumulative Survival Study Group [COPERNICUS]¹⁴ have used different beta-blockers. In patients with heart failure, beta-blockers represent a clear benefit for reducing mortality.

Nebivolol's utility in senior populations was addressed directly in the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial¹⁵; its 2,128 study participants were all older than 70 years (mean age 76 years) and had heart failure. This study more closely approximated a real-world population of heart-failure patients than did previous beta-blocker studies because its participants tended to be older. Most were male, and two thirds of them had clear systolic dysfunction. Most of them had been prescribed ACE inhibitors and diuretics, and approximately 40% were taking digoxin. Approximately 25% were also taking aldosterone antagonists.

The primary outcome measure—all-cause mortality or cardiovascular hospitalizations—was chosen to reflect quality of life in the elderly. Nebivolol dramatically reduced the risk for all-cause mortality and cardiovascular hospitalizations. Beneficial effects appeared after 6 months and were sustained with longer treatment durations. In participants younger than 75 years, nebivolol conferred clear benefit even when ejection fraction exceeded 35%. Nebivolol is effective and well tolerated in elderly patients with heart failure.¹⁵

Dr. Gonzalez: *Microalbuminuria is a marker for endothelial dysfunction. What do you believe nebivolol's effect on microalbuminuria would be?*

Dr. Bakris: Studies have not been done, but my opinion based on what I have seen to date is that its benefit would probably be more profound than that seen with carvedilol. Its antioxidant effect in combination with its NO effect should reduce microalbuminuria independent of blood pressure dramatically compared with other beta-blockers. It needs to be tested also against an ACEI. Its utility may be for the elderly who, if they have elevated creatinine levels, cannot take an ACEI, but we must wait for controlled studies to confirm this.

Dr. Gonzalez: *Our patient RM said when she presented that her glucose became more difficult to control after starting metoprolol XL. What message is in her insistence on this point?*

Dr. Bakris: We should listen to patients. Because, in fact, some of the best ideas I've had to build my career came from patients.

DISCLOSURES

This article is based on a presentation funded by an educational grant from Forest Pharmaceuticals. The authors disclose that they have received honoraria from Forest Pharmaceuticals for participation in this supplement. George L. Bakris discloses the following commercial/financial relationships through grant/research support, consultant services, speakers bureaus, and/or advisory boards: AstraZeneca, Abbott, Boehringer-Ingelheim, BMS/ Sanofi-Aventis, Kos, GlaxoSmithKline, Merck, Novartis, Lilly, Walgreens (Formulary Committee), NIH (NIDDK/NHLBI), and Atlas Foundation; Edgar R. Gonzalez discloses the following commercial/ financial relationships through grant/research support, consultant services, speakers bureaus, and/or advisory boards: Amgen and King Pharmaceuticals.

REFERENCES

1. American Diabetes Association. Standard of medical care in diabetes—2006. *Diabetes Care*. 2006;29(suppl):S4-S42.
2. Kjekshus J, Gilpin E, Cali G, Blackey AR, Henning H, Ross J Jr. Diabetic patients and beta-blockers after acute myocardial infarction. *Eur Heart J*. 1990;11:43-50.
3. Coreg [carvedilol, package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2007.
4. Bakris GL, Fonseca V, Katholi RE, et al; GEMINI investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA*. 2004;292:2227-36.
5. Jacob S, Rett K, Henriksen EJ. Antihypertensive therapy and insulin sensitivity: do we have to redefine the role of beta-blocking agents? *Am J Hypertens*. 1998;11:1258-65.
6. 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;8:127-34.
7. Vysouslis GP, Karpanou EA, Pitsavos CE, Skoumas JN, Paleologos AA, Toutouzias PK. Differentiation of beta-blocker effects on serum lipids and apolipoproteins in hypertensive patients with normolipidaemic or dyslipidaemic profiles. *Eur Heart J*. 1992;13:1506-13.
8. Data on file, Mylan-Bertek Pharmaceuticals, Inc.
9. Kakoki M, Hirata Y, Hayakawa H, et al. Effects of vasodilatory beta-adrenoceptor antagonists on endothelium-derived nitric oxide release in rat kidney. *Hypertension*. 1999;33(1 pt 2):467-71.
10. Doumas M, Tsakiris A, Douma S, et al. Beneficial effects of switching from beta-blockers to nebivolol on the erectile function of hypertensive patients. *Asian J Androl*. 2006;8:177-82.
11. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med*. 1996;334:1349-55.
12. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001-07.
13. CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomized trial. *Lancet*. 1999; 353:9-13.
14. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. Carvedilol Prospective Randomized Cumulative Survival Study Group. *N Engl J Med*. 2001;344:1651-58.
15. 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;26:215-25.

Pharmacoeconomic Benefits of Antihypertensive Therapy

Edgar R. Gonzalez, PharmD, FASHP, FASCP

ABSTRACT

BACKGROUND: Effective blood pressure reduction reduces cardiovascular risk and prevents later complications.

OBJECTIVE: To consider the pharmacoeconomic benefits of antihypertensive therapy.

SUMMARY: Every managed care pharmacist should consider the balance of cost and benefit of antihypertensive therapies, ensuring that best treatment options for patients with the lowest cost to the health care system are available and implemented. Pharmacists must also evaluate the direct and indirect cost associated with risk reduction for stroke and cardiovascular disease.

CONCLUSION: Using an interdisciplinary approach to hypertension treatment, pharmacists can assume a major role in detection, management, and control of hypertensive patients. As the medical teams' drug expert, they will be expected to recommend best treatment options for effective blood pressure control and cardiovascular risk reduction.

KEYWORDS: Pharmacoeconomic, Blood pressure, Cardiovascular disease, Hypertension, Metabolic syndrome, Nebivolol, Quality of life

J Manag Care Pharm. 2007;13(5):S20-S21

Effective blood pressure (BP) reduction reduces cardiovascular risk and prevents later complications. Every managed care pharmacist needs to consider the balance of cost and benefit, ensuring that best treatment options for patients with the lowest cost to the health care system are available and employed. We also must be careful to evaluate the direct and indirect costs associated with risk reduction for stroke and cardiovascular disease (CVD).

Cardiovascular Disease: The Costs

The National Institutes of Health provides a staggering statistic for the cost of cardiac disease in the United States. If one looks at coronary heart disease, the direct and indirect costs are approximately \$152 billion. Stroke management costs approximately \$63 billion, and hypertension and heart failure cost \$66 billion and \$33 billion, respectively. The emphasis on preventive measures in coronary artery disease and patients with multiple risk factors for stroke and heart failure is well placed.¹

To get a sense of the 10-year risk of fatal CVD with and without treatment with beta-blocker therapy and savings associated with beta-blocker therapy, Kaltwasser and colleagues² followed 8,682 hypertensive patients who received nebivolol 5mg/day. When a cardiovascular death occurred, they determined if the patient had been treated with a beta-blocker. The expected 10-year mortality rate from the Framingham Heart Study estimates that 30% of males and 36% of females die. This study found that 154 male deaths and 159 female deaths could have been avoided by beta-receptor blockade.

Calculating using the euro as a basis, these investigators examined economic impact. The table shows the cost per event and the total value of missed savings: 2.5 million euros or U.S.\$3.2 million.² These data show that nebivolol provides cost-effective therapy for patients with hypertension and coexisting cardiovascular comorbidities.

TABLE Potential Economic Impact of Treatment With Nebivolol 5 mg/Day

Event	Cases Avoided	U.S. Managed Care		United Kingdom	
		Cost per Event (Euro)	Cost Avoided (Euro)	Cost per Event (Euro)	Cost Avoided (Euro)
Stroke	150	8,620	1,013,323	2,285	268,613
CHD	94	19,962	1,470,555	2,250	165,752
Total			2,483,878		434,365

Only inpatient costs were considered.

Hospitalization costs (2004 values) were converted to the euro.

Kaltwasser MT. *Am J Cardiovasc Drugs*. 2005.²

CHD=coronary heart disease.

Author

EDGAR R. GONZALEZ, PharmD, FASHP, FASCP, is president, Capital Pharmacy Consultants, Mechanicsville, Virginia.

AUTHOR CORRESPONDENCE: Edgar R. Gonzalez, PharmD, FASHP, FASCP, President, Capital Pharmacy Consultants, 8315 Corbin Braxton Ln, Mechanicsville, VA 23111. Tel: (804)399-8482; Fax: (804) 799-3180; E-mail: ergonzalez@cpcllc.com

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.

Patients often believe that any asymptomatic disease and CVD specifically requires treatment that is often more problematic and more painful than the disease itself. Increasing the number of medications on the regimen or number of doses per day complicates matters further. The average patient with hypertension needs 2 to 3 antihypertensives to reach and maintain BP control.³ Once-daily hypertensive therapy can be quite helpful.

Maintaining Quality of Life

Must a good antihypertensive effect change quality of life? Researchers compared nebivolol 5 mg and the angiotensin II receptor blocker losartan 50 mg in a double-blind, randomized, parallel study of 314 patients with hypertension over 12 weeks. Both drugs were given once daily. If diastolic response was inadequate after 6 weeks, they added 12.5 mg of hydrochlorothiazide once daily. The drugs' effect on systolic BP was similar, but nebivolol decreased diastolic BP to a greater degree than did losartan. Significantly more losartan-treated patients required supplementary hydrochlorothiazide to achieve BP control than did those treated with nebivolol, thus increasing the number of drugs they were taking. Patients reported similar quality of life (including sexual function) at 6 and 12 weeks. Headache occurred more frequently in the losartan arm.⁴ Use of nebivolol may allow monotherapy to a greater extent, improving adherence and reducing copayment burden.

Quality improvement programs can help with adherence issues. Fonarow et al. organized pharmacists and nurses to promote appropriate medications for heart failure patients and to work with hospitalized patients before discharge.⁵ Called the Cardiac Hospitalization Atherosclerosis Management Program (CHAMP), it promoted initiation of aspirin, cholesterol-lowering medication, beta-blocker, and angiotension-converting enzyme inhibitor (ACEI) therapies. Hospital staff also counseled patients about diet and exercise at the time of hospital discharge. Treatment rates and clinical outcome were compared in patients discharged after myocardial infarction (MI) in the 2-year periods before and after program implementation. As a consequence of this intervention, aspirin use increased from 68% to 92%, beta-blocker use increased from 12% to 62%, ACEI use escalated from 6% to 58%, and statin use went from 6% to 86%. These improvements were sustained during the 6- to 18-month period after hospital discharge. A larger proportion of post-CHAMP patients (58%) lowered their low-density lipoprotein cholesterol to less than 100 mg/dL compared with only 6% of patients in the pre-CHAMP group. Recurrent MI and 1-year mortality also fell. Enhancing compliance is critical, as is selection of the appropriate therapy for these patients.

Summary

Managed care pharmacists can help patients with multiple risk factors and hypertension in several ways. Healthy People 2010 goals and Health Plan Employer Data Information Set 2006 measures for hypertension will require a much more aggressive approach to achieve desired BP control rates. That means pharmacists must monitor polypharmacy aggressively and become more vigilant for patient adherence. Using an interdisciplinary approach to hypertension treatment, pharmacists can assume a major role in detection, management, and control of hypertensive patients. They must identify and screen patients who may have metabolic syndrome. Their prescription records and medical databases will be used to track drug adherence, treatment control rates, optimal therapy, and overall compliance to therapy. As the medical teams' drug experts, pharmacists will be expected to recommend best treatment options for effective BP control and cardiovascular risk reduction.

DISCLOSURES

This article is based on a presentation funded by an educational grant from Forest Pharmaceuticals. The author discloses that he has received honoraria from Forest Pharmaceuticals for participation in this supplement. He discloses the following commercial/ financial relationships through grant/research support, consultant services, speakers bureaus, and/or advisory boards: Amgen and King Pharmaceuticals.

REFERENCES

1. Rosamond W, Flegal K, Friday G, and Writing Group Members. Heart disease and stroke statistics—2007 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. Epub. December 28, 2006;115:1-103.
2. Kaltwasser MT. Economic evaluation of nebivolol in the treatment of hypertension. *Am J Cardiovasc Drugs*. 2005;5:319-24.
3. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis*. 2000;36:646-61.
4. Van Bortel LM, Bulpitt CJ, Fici F, et al. Quality of life and antihypertensive effect with nebivolol and losartan. *Am J Hypertens*. 2005;18:1060-66.
5. Fonarow GC, Gawlinski A, Moughrabi S, et al. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). *Am J Cardiol*. 2001;87:819-22.

The Changing Landscape of Hypertension and the Evolving Role of Vasodilatory Beta-Blockers

Managed Market Resources is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. A total of 0.20 CEUs (2.0 contact hours) will be awarded and a continuing education statement will be sent to pharmacists for successful completion of this continuing education program, which is defined as receiving a minimum score of 70% on the posttest and completion of the Program Evaluation form. ACPE Universal Program No. 788-000-07-001-H01. (Release date: May 1, 2007; Expiration date: July 31, 2008)

Continuing Education for this program is processed solely through the AMCP.org Online Learning Center site at www.amcp.org (Learning Center/Online CE). No mailed forms will be accepted.

The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this program, you must complete the following forms online:

1. Posttest form for this program, "The Changing Landscape of Hypertension and the Evolving Role of Vasodilatory Beta-Blockers," on the AMCP.org Online Learning Center site-to receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.
2. Program Evaluation form

Upon successful completion of this program, you will automatically receive your CE statement. Your CE credits will be automatically archived and tracked for you on the AMCP.org Online Learning Center site. All information is kept confidential.

Posttest Worksheet: The Changing Landscape of Hypertension and the Evolving Role of Vasodilatory Beta-Blockers

1. Which of the following statements about hypertension is false?
 - a. One in 3 American adults has hypertension.
 - b. The lifetime risk of developing hypertension is greater than 90%.
 - c. Blood pressure of 140/90 mm Hg does not pose an increased risk for cardiovascular disease.
 - d. The target blood pressure goal for patients diagnosed with hypertension is less than 140/90 mm Hg.
2. According to JNC 7 guidelines, which of the following statements about blood pressure is true?
 - a. Hypertension is classified as stage 1 (blood pressure 120/80 mm Hg), stage 2 (120-139/80-89 mm Hg), stage 3 (140-159/90-99 mm Hg), and stage 4 ($\geq 160/\geq 100$ mm Hg).
 - b. Blood pressure is classified as normal (<120/<80 mm Hg), prehypertension (120-139/80-89 mm Hg), stage 1 hypertension (140-159/90-99 mm Hg), and stage 2 hypertension ($\geq 160/\geq 100$ mm Hg).
 - c. Blood pressure is classified as normal (130/80 mm Hg), stage 1 (140-159/90-99 mm Hg), or stage 2 ($\geq 160/\geq 100$ mm Hg).
 - d. Blood pressure is classified as normal (<110/<70 mm Hg), prehypertension (110-129/80-89 mm Hg), stage 1 hypertension (130-149/90-99 mm Hg), and stage 2 hypertension ($\geq 150/\geq 100$ mm Hg).
3. Throughout life, systolic (but not usually diastolic) blood pressure increases.
 - a. True
 - b. False
4. Which of the following statements about blood pressure is false?
 - a. After age 50 to 60 years, systolic blood pressure decline is associated with increased large artery stiffness.
 - b. Systolic blood pressure elevation may worsen artery stiffness.
 - c. In advanced age, both diastolic and systolic blood pressure should be used as a risk assessment tool.
 - d. Coronary heart disease risk rises as systolic blood pressure rises.

5. The relative risk of cardiovascular death in patients with kidney disease or end-stage renal disease is
 - a. 1.5.
 - b. 2.7.
 - c. 3.4.
 - d. 2.8.
6. A patient with metabolic syndrome
 - a. must have 4 or more of the following: obesity, low HDL-Cs, a blood pressure above 130/85 mm Hg, elevated triglycerides, and elevated fasting blood glucose.
 - b. is at an increased risk for diabetes and cardiovascular disease.
 - c. is more likely to be African American.
 - d. is more likely to be Caucasian.
7. Which of the following statements is false?
 - a. Obesity has a higher prevalence in males aged 12 to 19 years.
 - b. Excessive weight causes insulin resistance.
 - c. Metabolic syndrome is an interplay of blood pressure, elevated liver enzymes, and obesity.
 - d. Approximately one third of Americans between the ages of 50 and 59 years have metabolic syndrome.
8. Which of the following statements about the endothelium is false?
 - a. The endothelium is a single cell lining that has a very small role in the production of compounds affecting cardiovascular function.
 - b. The endothelium is a group of cells that produce compounds important in regulating vascular homeostasis.
 - c. The endothelium is a huge, living organ that has more cells than the liver, which is the largest organ in the body.
 - d. The endothelium maintains normal blood viscosity, prevents abnormal blood clotting, and prevents abnormal bleeding.
9. Nitric oxide
 - a. and its role as the signaling molecule in the cardiovascular system was discovered by Robert Furchott, Louis Ignarro, and Ferid Murad.
 - b. is also known as endothelial-derived relaxing factor.
 - c. produces vasorelaxation by stimulating guanylate cyclase pathway in the smooth muscle cells.
 - d. All of the above are correct.
10. Which of the following statements is false?
 - a. Normal endothelium limits vasculature inflammation and suppresses smooth muscle cell proliferation.
 - b. Abnormal endothelium causes a decrease in vasoconstriction with decreased nitric oxide formation and decreased angiotensin I and prostaglandin formation.
 - c. Abnormal endothelium promotes thrombosis and vasoconstriction.
 - d. Hypertensive patients lose their ability to vasodilate normally.
11. Panza and colleagues concluded that clinically effective antihypertensive treatment restores impaired endothelium-dependent vasodilation in hypertensive patients.
 - a. True
 - b. False
12. Which of the following study findings is true, from the study performed by Murakami and colleagues?
 - a. 23% of patients in the lower tertile experienced cardiac death, myocardial infarction, worsening angina, or the need for revascularization.
 - b. 7% of patients in the middle tertile experienced cardiac events.
 - c. No patients in the upper tertile experience cardiac events.
 - d. All of the above are true.
13. All of the following are true *except*
 - a. Insulin-mediated and endothelium-dependent vasodilation is impaired in obesity, hypertension, and non-insulin-dependent diabetes mellitus.
 - b. Endothelial dysfunction in patients with non-insulin-dependent diabetes mellitus may worsen insulin resistance, increase vascular reactivity, and encourage macrovascular disease.
 - c. Patients with diabetes and hypertension have decreased plasma levels of von Willebrand factor.
 - d. Patients with diabetes and hypertension have reduced nitric oxide release and responsiveness.
14. Which amino acid is involved in nitric oxide production?
 - a. L-alanine
 - b. L-arginine
 - c. L-asparagine
 - d. L-aspartic acid

15. Lifestyle changes that may prevent endothelial dysfunction include all of the following *except*
 - a. smoking cessation.
 - b. weight loss.
 - c. regular exercise.
 - d. increasing dietary fat consumption.
16. All of the following are true statements *except*
 - a. A sign of endothelial dysfunction is the presence of microalbuminuria.
 - b. Microalbuminuria indicates subclinical cardiovascular disease.
 - c. Stimulating beta-receptors causes vasoconstriction.
 - d. Beta-receptors predominate in healthy cardiac muscles and beta₂ receptors predominate in the lungs.
17. Nebivolol
 - a. is a traditional beta-blocker.
 - b. is a long-acting beta₁ selective with endothelial-dependent vasodilation associated with activation of the L-arginine/nitric oxide pathway.
 - c. is a long-acting nonselective beta-blocker with intrinsic sympathomimetic activity.
 - d. is associated with decreased insulin sensitivity.
18. All of the following statements are true *except*
 - a. Beta-blocker subclasses appear to differ significantly in antihypertensive efficacy.
 - b. Beta-blockers with intrinsic sympathomimetic activity have fewer clinical benefits in post-MI patients and precipitate heart failure in high-risk patients.
 - c. Beta-blockers differ in terms of benefit/risk in diabetes and insulin sensitivity.
 - d. Third-generation beta-blockers improve insulin sensitivity.
19. In a 12-week, double-blind study in middle-aged people with mild-to-moderate hypertension who were randomized to nebivolol or atenolol,
 - a. nebivolol was shown to be more efficacious in controlling blood pressure than atenolol.
 - b. nebivolol caused more bradycardia than atenolol.
 - c. nebivolol had the same effect on sitting blood pressure as atenolol.
 - d. nebivolol was better tolerated and study subjects reported fewer side effects than subjects on atenolol.
20. In an observational study evaluating 6,376 adult subjects with arterial hypertension treated with nebivolol, researchers found that
 - a. at the end of 6 weeks, 62.2% of the patients on nebivolol reached normal blood pressures.
 - b. in diabetics, triglycerides fell by 18% and cholesterol by 9%, and in nondiabetics, triglycerides fell by 13% and cholesterol by 8%.
 - c. the study concluded that nebivolol monotherapy improves glucose and lipid parameters even in patients with diabetes.
 - d. All of the above are correct

To complete this activity, go to www.amcp.org (Learning Center/Online CE), where you will access the posttest and evaluation form.

NOTES

[illegible]

Supplement