

# JMCP

JOURNAL OF MANAGED CARE PHARMACY®

## An Evidence-Based Approach: The Emerging Role of Renal Protection in Hypertension; A Focus on Clinical and Economic Factors That Impact Formulary Decision Making

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## Supplement

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Continuing Education Program

# JMCP

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Hunsicker's research has focused on the areas of progressive renal disease, transplantation medicine, the design and performance of clinical trials, and the analysis of large national medical databases. In 1979, he and Dr. Edmund Lewis of Chicago founded the Collaborative Study Group (CSG), a consortium of nephrologists that now has members worldwide. Hunsicker is a member of the CSG Executive Committee and principal investigator of the Data Center for the Type 2 Diabetes Study.

Recently appointed chair of the United Network for Organ Sharing/University Renal Research and Education Association (UNOS/URREA) Data Working Group, Hunsicker is also the principal investigator for the Economic Special Studies Center of the United States Renal Data System. A founder and past president of the American Society of Transplantation, he was awarded the society's Roche Lifetime Achievement Award. He has served as president of the American Council on Transplantation, National Kidney Foundation of Iowa, and UNOS. He was a regional president of the National Kidney Foundation, the first medical advisor to the American Organ Procurement Organization, and a member of the Department of Health and Human Services Secretary's Advisory Committee on Organ Transplantation. He has been a member and chair of numerous National Institutes of Health study sections and is a member of the U.S. Food and Drug Administration Advisory Committee on Antivirals.

# Supplement Policy Statement

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

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During his 30-year career in pharmacy, including 20 years specializing in managed care, Orland has developed clinical intervention programs and new prescription benefit programs, established programs to monitor physician prescribing practices and initiatives to educate physicians on quality and cost-effective prescribing, and worked with the pharmaceutical industry to develop value-added programs. He previously held management positions with Harvard Pilgrim Health Care, NYLCare, and Fallon Clinic, Inc.

A charter member of the Academy of Managed Care Pharmacy, Orland is also a member of the American Society of Hospital Pharmacists, American Pharmaceutical Association, Retail Pharmacists Association, and the Massachusetts Society of Hospital Pharmacists. He was the first representative of the managed care industry to serve on the Massachusetts Board of Registration in Pharmacy.

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Rodby was named one of the Best Doctors in America in 2001 and one of America's Top Physicians by the Consumers' Research Council of America in 2003. He is an assistant editor for *Seminars in Dialysis*, and he reviews manuscripts for numerous medical publications, including *American Journal of Kidney Disease*, *Archives of Internal Medicine*, and *PharmacoEconomics*. Rodby has written 12 book chapters and published more than 50 articles in peer-reviewed journals.

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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.

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# The Importance and Impact of Evidence-Based Medicine

SONYA J. LEWIS, RPh, MBA, and BURTON I. ORLAND, BS, RPh

## ABSTRACT

**OBJECTIVE:** To describe the new paradigm of evidence-based medicine (EBM) and the benefits of using EBM in making treatment decisions for individual patients.

**SUMMARY:** Applying the knowledge gained from large clinical trials to patient care promotes consistency of treatment and optimal outcomes, helps establish national standards of patient care, and sets criteria to measure and reward performance-based medical practice. Implementing the principles of EBM, which rely on the rules of evidence and research, requires a commitment from medical schools, local health and medical licensing departments, physicians, pharmacists, professional associations, and managed care organizations. A review of results from landmark trials in hypertension, diabetic nephropathy, and end-stage renal disease describes the research for evidence-based therapies. A review of studies in the pharmacist's expanding role in implementing evidence-based medicine shows the benefits of collaborative medical practices.

**CONCLUSION:** Implementation of EBM in the managed care setting provides standards that have the potential to provide the best medical care at the lowest cost.

**KEYWORDS:** Evidence-based medicine, Managed care organization (MCO), Treatment guidelines, Performance-based medicine, Cost-effective formulary, Clinical trials, Primary care team, Therapy

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### Target Audience

Pharmacists, formulary decision makers, physicians, and nurses in a managed care environment

### Learning Objectives

Upon completion of this program, participants will be able to

1. outline strategies for the long-term management of hypertension and review American Diabetes Association (ADA) and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines;
2. discuss the evidence-based JNC 7 guideline recommendations and the application of these findings in patients with type 2 diabetes and kidney disease;
3. summarize the results of the 3 clinical trials that examined the effects of angiotensin II receptor blockers on the progression of renal disease in patients with type 2 diabetes;
4. differentiate the mechanism of action of angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors; and
5. evaluate the cost-effectiveness of angiotensin II receptor blocker therapy for controlling hypertension and diabetic nephropathy.

## The Importance of Evidence-Based Medicine

If one needs to describe evidence-based medicine (EBM), David Sackett, a pioneer in the field, defined it succinctly as “. . . the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.” It can also be said that EBM uses scientific evidence that is rigorously obtained—and this contrasts with anecdotal experience, which can be biased, since even the most knowledgeable physician can be influenced in the decision-making process by recent experience with patients. Bias, however, can be overcome if the physician is attuned to the results of large, controlled, and objective clinical studies upon which to base treatment strategies. This approach is known as evidence-based medicine.<sup>1</sup>

The advantage of EBM is that the knowledge gained from large clinical trials is applied directly to patient care. Use of EBM promotes consistency in individual patient treatments that assume optimal clinical outcomes and improved quality of life. A main benefit of EBM is its use in the development of evidence-based treatment guidelines. When discussing prescribing patterns, the guidelines make it more efficient to review treatment strategies with physicians, discuss the value of the guidelines for managed care organizations (MCOs), and promote cost-effective formulary decisions. With EBM to support organizational clinical policies, physician agreement on documented clinical evidence can be much more easily achieved.<sup>2</sup>

Considering that the average physician has 7 or 8 MCO affiliations, it becomes apparent that the benefits of EBM can have a far-reaching effect on all of a physician's patients. Using Hibbing Economic Development Authority and National Committee for Quality Assurance criteria for the credentialing of physicians provides a level of consistency that defines a high standard of care for all patients. Using EBM in physician practices maintains regional consistency among MCO members so that national standards can be upheld. Further, excellence in medical practice can be measured with EBM—performance-based medicine can be implemented and physicians can be rewarded

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with either enhanced reimbursement or high capitation that reflects the value of using EBM.<sup>2</sup> The bottom line with EBM is that it provides the best doctors and the best medicine at the lowest cost, which means that consistency of care is maintained.<sup>2</sup>

### ■ Evidence-Based Medicine Is a New Paradigm in Treatment Strategies

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EBS is, in fact, the new paradigm for medical practice. This new model deemphasizes intuition, unsystematic clinical experience, and the use of pathophysiology as the foundation for making clinical decisions. Instead, EBM emphasizes the importance of the results of large clinical trials in formulating individual treatment strategies. The use of EBM also requires new skills on the part of the physician. These include frequent and efficient literature searches and the critical use of established rules of evidence for evaluating clinical literature.<sup>3</sup>

The older paradigm of medical practice gave physicians a variety of options to sort out clinical problems. Physicians drew on their own clinical experience, reflected on their knowledge of the underlying pathophysiology, researched in a textbook, or referred cases to local experts in the field. Answers to difficult clinical presentations were often pursued through direct contact with local specialists. This particular paradigm puts a high value on the concept of traditional scientific authority and adherence to recognized approaches to treatment. The newer approach, EBM, makes certain assumptions that do not reflect the older ways of clinical thinking.<sup>3</sup>

Certain established teaching methods are still held in high esteem in the new paradigm. Clinical experience and the development of clinical diagnostic instincts are still crucial and important in becoming a competent physician. However, systematic attempts to record reproducible observations in an unbiased manner (the scientific method) strongly increase the confidence that the physician can have in a prognosis, the value of prognostic testing, and the efficacy of treatment strategies. Without systematic and reproducible observation, the clinician must be cautious, as the interpretation of information gleaned from clinical experience and intuition alone may be misleading. Indeed, an understanding of the pathophysiology of any disease state is invaluable, but that understanding is an insufficient guide for formulating treatment strategies and may lead to inaccurate predictions about the performance of diagnostic tests and the effectiveness of treatment modalities. It is therefore important that the rules of evidence be understood in order to correctly interpret the literature on causation of disease, prognosis, diagnostic testing, and therapy planning.<sup>3</sup>

### ■ Teaching Evidence-Based Medicine

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More timely adoption of EBM by physicians may require 2 dramatic steps. First, all medical schools in the United States should be required to teach EBM to their students. Currently, only 9% (11 of 125) of medical schools offer a separate course on EBM.

As a follow-up, when students graduate and enter residency programs, continuing medical education throughout their careers should reinforce the EBM training.<sup>4</sup>

Acting as role models, attending physicians should be enthusiastic and effective in conveying the importance of EBM, especially to residents and other attending doctors. Role models impart attitudes that help learners develop skills in critical appraisal. The physician role model is important insofar as the mentoring involves focus on the importance of the strength of evidence supporting clinical decisions that are derived from the findings of large, randomized, controlled clinical trials. The mentor can also cite large, randomized studies that have been rigorously reviewed and included in a focused meta-analysis. In other instances, the best evidence may still come from accepted practice or a physician's clinical experience and instincts. The clinical mentor should always clearly identify the basis on which treatment decisions are being made in a particular case.<sup>3</sup>

Second, the EBM training should be enforced. State health departments or professional associations could monitor physicians' adherence to guidelines to ensure compliance. This would be especially applicable for illnesses such as diabetes, heart disease, hypertension, asthma, and chronic obstructive pulmonary disease. The MCOs may also participate by monitoring the doctors within their networks. Suspension of licensing might be a final measure with nonadhering practitioners.<sup>4</sup>

### ■ The Effectiveness of Evidence-Based Medicine

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Measuring physician treatment practices and patient outcomes can, however, be a challenge. Patients vary in complexity and degree of illness, as they do in their individual responses to medication and other treatment modalities, so statistical data must be gathered properly and then corrected to reflect variations in patient complexity. Ultimately, though, EBM will help physicians provide more rational care with better outcomes. The guidelines based on large, randomized, controlled studies are not inflexible, and they do provide the best first step. Patients are still treated on an individual basis, especially in cases of serious illness or when issues requiring treatments are not specifically covered by guidelines. That is when the physician's judgment and years of medical training become invaluable assets.<sup>3</sup>

The proof of EBM rests on whether patients who are treated in this mode enjoy better health. Of course, this proof is no more available for the new paradigm than for the old—simply because at this time, there have not been any long-term comparative studies. What do exist are data from short-term trials confirming that the skills of EBM can be taught to students in medical schools and to residents.<sup>3</sup>

### ■ The Future of Evidence-Based Medicine

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EBM is concerned directly with the uncertainties of clinical medicine but has the potential to transform the next generation of

clinicians.<sup>3</sup> These new physicians will join their established colleagues in facing a profusion of scientific literature, the continuous introduction of highly complex technologies, concern about the escalating costs of medical care, and an increased awareness of both the quality of positive outcomes and treatment strategies. All indicators point to EBM as a paradigm that will help deal with many of those issues. Because EBM will require new skills and outlooks for clinicians, incorporating the principles of EBM into postgraduate medical training and residency education should promote the dissemination of this new way of developing treatment strategies. The ultimate objective is that EBM will become totally integrated into the daily practice of medicine.<sup>3</sup>

### ■ The Impact of Evidence-Based Medicine on Outcomes and Costs

The articles that follow present data from important research: the Collaborative Study Group (CSG) early trial, the Irbesartan Diabetic Nephropathy Trial (IDNT), the Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) trial, and the Irbesartan in Patients with Type II Diabetes and Microalbuminuria (IRMA II) trial. These clinical trials are examples of large, randomized, controlled studies that produced data that can be used to develop evidence-based treatment strategies for patients with type 1 or type 2 diabetes who are progressing to end-stage renal disease.

The landmark studies cited in these articles were conducted using angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in the treatment of hypertension, end-stage renal disease, and diabetic nephropathy. The resulting data show that blockade within the renin-angiotensin-aldosterone system axis and adherence to the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the American Diabetes Association in the management of hypertension and microalbuminuria in type 2 diabetes and overt diabetic nephropathy produced excellent patient outcomes. These data also show that treatments with ACE inhibitors and ARBs were cost effective, improved quality of life for many patients, and, in some cases, prolonged lives from months to years.

From a managed care point of view, these trial data indicate that the health of these patients can be improved and the costs of treatment can be reduced through implementation of EBM in their treatment plans. Now that the effectiveness of ACE inhibitors and ARBs has been studied and the evidence examined with the goal

of devising the best strategies for this difficult-to-treat patient population, the critical challenge becomes the development of EBM guidelines and application of those guidelines in clinical practice.

The expanding collaborative role of pharmacists in implementing evidence-based treatment strategies is also discussed in the following articles. Results from several programs and studies involving patients with hypertension document the effectiveness of pharmacists as academic detailers, clinical advisors, and patient comanagers with physicians and primary care teams that utilize the EBM paradigm for treating patients with hypertension.

Development of evidence-based treatment strategies, education and training of physicians who are adept at evaluating the literature with an EBM perspective, and acceptance of and adherence to EBM policies by physicians and pharmacists in a collaborative mode are critical to attaining better outcomes for patients with diabetes, hypertension, and other complex, chronic diseases. The EBM paradigm is poised to have a positive impact in the managed care setting—providing the best medical care at the lowest cost and achieving optimal outcomes.

### DISCLOSURES

This article is based on the proceedings of a satellite symposium held March 31, 2004, at the Academy of Managed Care Pharmacy's 16th Annual Meeting and Showcase in San Francisco, California, which was funded by an unrestricted educational grant from Bristol-Myers Squibb Company and Sanofi-Synthelabo Inc. partnership. Authors Sonya J. Lewis and Burton I. Orland received an honorarium from Bristol-Myers Squibb Company and Sanofi-Synthelabo Inc. partnership for participation in the symposium upon which this article is based; they disclose no potential bias or conflict of interest relating to this article.

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# Pharmacoeconomic Challenges in the Management of Diabetic Nephropathy

ROGER A. RODBY, MD

## ABSTRACT

**BACKGROUND:** Diabetes is the most common cause of end-stage renal disease (ESRD)—kidney failure to the point of requiring dialysis or a kidney transplant—representing 45% of all new patients enrolling into ESRD programs. Approximately 400,000 patients in the United States have ESRD, and this number has doubled over the decade from 1991-2001. Dialysis is a very expensive modality costing more than \$50,000 per patient per year. Total medical spending for the 400,000 patients with ESRD cost \$22.8 billion in 2001, an almost 3-fold increase over the same 1991-2001 decade. ESRD spending represents 6.4% of the total Medicare budget, a 33% increase from 4.8% in 1991. This epidemic growth in ESRD has led to skyrocketing utilization of health care resources.

**PURPOSE:** To summarize the (1) economic impact of the increased prevalence and costs associated with ESRD secondary to diabetes, (2) major evidence in diabetic nephropathy associated with the use of agents that block the renin-angiotensin-aldosterone system (RAAS) to delay the progression to ESRD, and (3) results of a recent pharmacoeconomic analysis on the economic impact of the use of the angiotensin receptor blocker (ARB) irbesartan to block the RAAS in diabetic nephropathy.

**RESULTS:** Application of pharmacoeconomic models demonstrate that use of irbesartan increases mean life expectancy from months to years, depending on when in the course of the disease irbesartan therapy is started. Further, use of this agent produces these results while lowering costs, with mean savings of \$3,000 to \$12,000 per patient.

**CONCLUSION:** Clinical trials show that blocking the RAAS with ARBs and angiotensin-converting enzyme inhibitors delays the progression of diabetic nephropathy to ESRD. Recent analyses using predictive models have concluded that the most effective strategy is to begin therapy early in disease progression.

**KEYWORDS:** Microangiopathy, Glomerulosclerosis, Diabetic nephropathy, Retinopathy, End-stage renal disease (ESRD), Albuminuria, Proteinuria, Renin-angiotensin-aldosterone system (RAAS), Irbesartan, Amlodipine, Medicare, Collaborative Study Group (CSG), Irbesartan Diabetic Nephropathy Trial (IDNT), Irbesartan in Patients with Type II Diabetes and Microalbuminuria (IRMA II) trial, Reduction of End Points in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) trial

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Diabetes is the most common cause of end-stage renal disease (ESRD), defined as kidney failure to the point of requiring renal dialysis or kidney transplantation. Diabetes-based ESRD accounts for nearly 45% of all new patients enrolled in ESRD treatment programs.<sup>1</sup> The number of people in the United States with ESRD has doubled between 1991 and 2001, and approximately 400,000 currently have the disease.<sup>1</sup> ESRD is very costly to manage, with costs that exceed \$50,000 per patient per year. In 2000, expenditures for the almost 400,000 patients with ESRD in the United States totaled about \$20 billion.

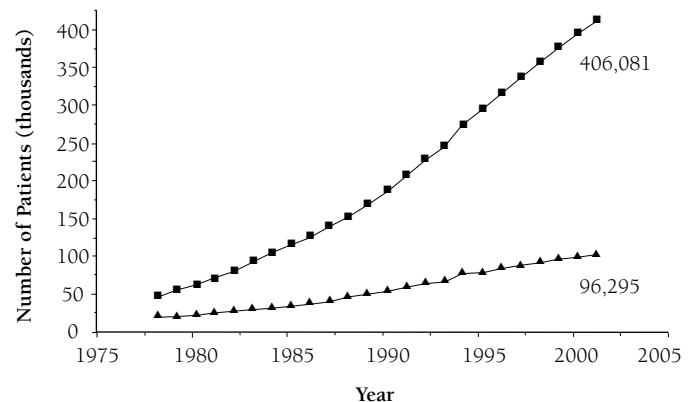
About 43% of ESRD patients have diabetes, and more than 90% of those patients have type 2 disease. The ESRD patient population is expanding rapidly and is projected to reach 650,000 in the United States by 2010, with resulting expenditures estimated to be approximately \$28 billion.<sup>2</sup> Pharmacologic blockade of the renin-angiotensin-aldosterone system (RAAS) has become the standard of care for patients with type 2 diabetes mellitus (DM) and renal involvement, markedly slowing progression to ESRD.<sup>3</sup> However, even pharmacotherapy to block the RAAS means additional costs to the health care system, and these costs must be balanced against treatment costs for ESRD.

## Economic Impact of Diabetic Nephropathy

### Growth in Diabetic and End-Stage Renal Disease Populations

Factoring in the aging of the baby boom population and the resulting expected growth in the diabetic and minority populations, projections are that, by the year 2030, more than

**FIGURE 1** ESRD Growth: Patients



▲ Incident ESRD ■ Prevalent ESRD

ESRD = end-stage renal disease.

Adapted from U.S. Renal Data System Annual Report 2003.<sup>1</sup>



2.2 million people in the United States—more than 1.3 million with DM and 945,000 without DM—could be at risk for developing ESRD. Consuming an ever-increasing portion of Medicare funds, these patients accounted for 6.4% of the 2003 budget, a 33% increase over 1991 expenditures.

By 2001, expenditures for the ESRD program had reached \$22.8 billion, with Medicare spending 11.5% higher than in 2000. This growth in expenditure is related primarily to increases in the use of dialysis injectables, including erythropoietin (EPO) and intravenous (IV) vitamin D and iron. In 2001, 96,285 new patients entered the ESRD program, bringing the annual total to 406,081—292,215 receiving dialysis and 113,866 with a functioning renal transplant.<sup>1</sup> Figure 1 shows the increase in both incidence and prevalence of ESRD over a 19-year period.<sup>1</sup> Figure 2 shows Medicare spending that includes paid claims, estimated Medicare+Choice costs, and estimated cost to obtain organs. Non-Medicare spending includes cost estimates for non-Medicare ESRD patients and estimates of patient obligations.<sup>1</sup>

### Diabetic Nephropathy and End-Stage Renal Disease

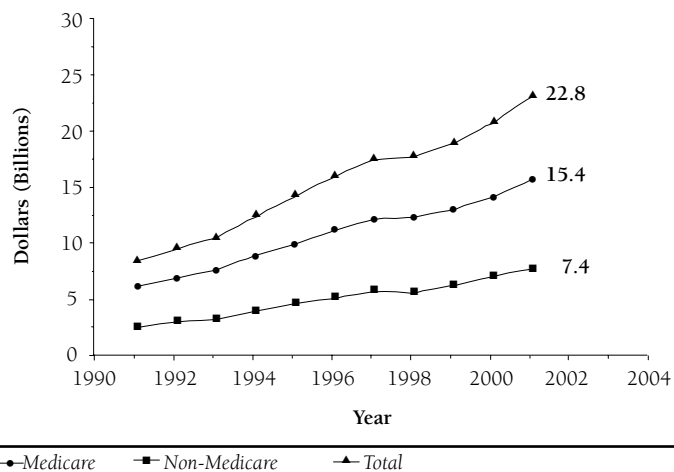
Diabetic nephropathy (DN) is the leading cause of ESRD in the United States and a leading cause of DM-associated morbidity and mortality. Albuminuria in patients with DM is associated with severely reduced survival and an increased risk of cardiovascular disease. Patients with DN frequently have concurrent morbidity associated with retinopathy and neuropathy. Although not completely understood, the mechanisms by which hyperglycemia leads to ESRD include structural changes in the glomerulus (glomerulosclerosis, mesangial expansion, basement membrane thickening, increased extracellular matrix), hemodynamic changes in renal microcirculation (increased glomerular capillary pressure, glomerular hyperfiltration), and interaction of soluble factors and cytokines (growth factors, angiotensin II, endothelin). Many of these effects may be altered through the use of agents that block the RAAS.<sup>4</sup>

The first clinical manifestation of DN is the appearance of small amounts of albumin in the urine, a condition known as microalbuminuria. This occurs as soon as 5 years after the diagnosis of DM. As the disease progresses, albuminuria increases and renal failure develops, eventually progressing to ESRD. This pre-ESRD stage is called overt nephropathy and can occur within 10 years after the diagnosis of DM.<sup>4</sup> Approximately 30% of patients with type 1 DM develop nephropathy. DN was once considered a less common complication of type 2 DM than type 1 DM. With improved treatments, more patients with type 2 DM survive to experience ESRD, and type 2 DM now represents the most common cause of ESRD.<sup>5</sup> As the incidence of DM is growing at epidemic proportions, so is the expected incidence of ESRD and costs related to type 2 DM.

### Pharmacoeconomics of Diabetic Nephropathy

In 1991, costs for ESRD were \$8 billion—\$5.8 billion in Medicare funds and \$2.2 billion in non-Medicare expenditures

**FIGURE 2** ESRD Growth: Expenditures



ESRD = end-stage renal disease.

Adapted from U.S. Renal Data System Annual Report 2003.<sup>1</sup>

from second- and third-party payers and other coverage. By 2001, costs of the ESRD program had risen to \$22.8 billion—nearly triple the earlier level. As a point of comparison, during the same time period, the entire Medicare budget merely doubled. The portion of the Medicare budget apportioned to ESRD is currently 6.4% of the entire \$242 billion budget, representing a 33% increase over the past 11 years. The Balanced Budget Act of 1997 extended the application of Medicare to 30 months as a secondary payer for patients with ESRD, a provision that applies to individuals in employer health plans. Larger numbers of patients are now covered by private insurers for at least the first 3 years of treatment. The economic burden of ESRD is demonstrated by the fact that non-Medicare spending has grown from \$2.2 billion in 1991 to \$7.4 billion in 2001 (Figure 2), representing a 237% increase in 1 decade.<sup>1</sup>

The U.S. government achieved its objective to reduce the economic burden of younger ESRD patients in the Medicare program by having those patients covered by the private sector. However, because of the ongoing shortage of kidneys available for transplantation into this younger population—thus providing ESRD care at a lower cost as well as yielding improved outcomes—dialysis treatments continued to be required for more patients. Recent per-patient-per-year (PPPY) and total program expenditures for ESRD have increased at rates not seen since the early 1990s. From 2000 to 2001, total spending for ESRD treatment grew by 11.5%.<sup>1</sup>

### Costs of Dialysis Therapy

Dialysis is a very expensive modality costing more than \$50,000 PPPY.<sup>1</sup> Total spending for the 400,000 patients with ESRD cost

\$22.8 billion in 2001. This enormous growth in ESRD expense has resulted in skyrocketing use of health care resources. Any treatment modality that could slow or prevent progression to ESRD would significantly affect health care spending. Further, expenditures for outpatient dialysis therapy have consistently outpaced inpatient costs. These cost gaps are expanding and include EPO and IV agents such as antibiotics, L-carnitine, vitamin D, and iron. Trends in increased costs for EPO are clear, and rapid growth is predicted in costs for IV vitamin D and iron. These trends in outpatient costs affect the entire panoply of payer groups. In the aging population dependent upon Medicare, the steady trend upwards for all expenditures continues.<sup>1</sup>

### **Cost Impact of the Aging of the End-Stage Renal Disease Population, Diabetes, and Increased Survival**

Improved survival rates and the increased age of the ESRD population have also resulted in increased expenditures. This upward movement has been led by proportionate increases in costs for patients aged 45 to 64 years and patients aged 75 years and older. Increases in health care burdens are also fueled by longer survival rates in minority populations and particularly in African Americans, who have a disproportionately higher program cost compared with the white population. Further, patients with ESRD caused by diabetes consume a larger portion of the ESRD program budget. When projected over the next 30 years, with the trends in both the general and ESRD populations continuing to rise at current rates, these patients will represent an increasingly larger economic burden and a challenge for all payers.<sup>1</sup>

### **Medicare and End-Stage Renal Disease**

The ESRD population using Medicare benefits grew at a rate of 4% between 2000 and 2001. However, the number of non-Medicare patients with ESRD increased by 8% during the same period. Based on the use of nondialysis services, estimates are that other medical costs were generated at a comparable rate. Growth in billed services for patients aged 0 to 19, 20 to 44, and 45 to 65 years (starting in 1999) appeared to reflect major and uniform changes in provided billing practices. According to primary diagnosis, recent increases are most apparent in the diabetic population (14.1%) and less for patients with a primary diagnosis of only hypertension (11.8%). The lowest costs are for patients with glomerulonephritis (7.1%) and other causes of ESRD (8.9%).<sup>1</sup>

The present economic burden of ESRD secondary to diabetes is overwhelming. As growth of this population continues to accelerate, future funding considerations become daunting. Fortunately, medical trials have led to therapies that slow and possibly even prevent progression to ESRD and thus have the potential to significantly impact these financial considerations.

## **Results**

### **Medical Treatment to Slow or Halt Progression to End-Stage Renal Disease in Type 2 Diabetes Mellitus**

In 1993, the Collaborative Study Group (CSG) reported on a clinical trial that demonstrated captopril, an angiotensin-converting enzyme (ACE) inhibitor, protected against deterioration of renal function in patients with type 1 DM and DN and was significantly more effective than blood pressure (BP) control alone.<sup>6</sup> This trial demonstrated that the use of captopril reduced the risk of doubling of the serum creatinine (a surrogate for progression to ESRD) by 48% when compared with standard antihypertensive therapy. Both treatment groups had similar BPs, thus the effect of captopril on progression was determined to be independent of its antihypertensive properties, an effect termed “renoprotection.”<sup>6</sup>

In 2001, the CSG reported on the Irbesartan Diabetic Nephropathy Trial (IDNT), which was designed to ascertain whether the use of the angiotensin-II receptor blocker (ARB) irbesartan or the calcium channel blocker (CCB) amlodipine provided similar renoprotection in overt nephropathy associated with type 2 DM.<sup>7</sup> In this trial, the use of irbesartan was shown to reduce the risk of doubling the serum creatinine by 33% when compared with standard antihypertensive therapy and by 37% when compared with treatment with the amlodipine. BPs were again similar across groups, indicating that these salutary effects were a result of renoprotection.<sup>7</sup> Similar results were reported using losartan in the Reduction of End Points in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) trial.<sup>8</sup>

Results of the Irbesartan in Patients with Type II Diabetes and Microalbuminuria (IRMA II) trial were also published in 2001. IRMA II studied the effects of the use of irbesartan (300 mg/day or 150 mg/day versus placebo) to prevent progression from the earlier stage of microalbuminuria to the later stage of overt nephropathy in patients with hypertension and type 2 DM. The study demonstrated that patients receiving irbesartan (300 mg/day) had about one third the risk of developing overt nephropathy compared with the patients not receiving (adjusted risk reduction 68% at 300 mg/day).<sup>9</sup>

### **Economic Impact of Blockade of Renin-Angiotensin-Aldosterone System in Diabetic Nephropathy**

The data from the 1991 CSG captopril trial in type 1 DN allowed the creation of a Markov pharmacoeconomic model to assess the economic impact of the use of captopril in patients with type 1 DM and overt nephropathy. Because progression was limited by captopril, the model predicted that this treatment resulted in an absolute direct cost savings of \$32,550 per patient and prolonged life by 2.15 years over the course of a lifetime compared with standard antihypertensive therapy.<sup>10</sup> These findings—prolonging life while saving money—are unusual in this day and age of escalating medical expenditures, but they become a recurring theme, as is demonstrated in subsequent pharmacoeconomic studies.

In the CSG's more recent study of the use of irbesartan in type 2 DM, a similar Markov predictive model was created to simulate the treatment of hypertensive patients with type 2 DM who had overt nephropathy similar to those patients enrolled in the IDNT. The model included 3 treatment arms (irbesartan, amlodipine, and placebo) and 5 primary health states: survive (entry state), 3 health states corresponding to the progression of DN (doubling of serum creatinine [DSC]), ESRD managed with dialysis (ESRD/dialysis), ESRD treated with renal transplant (ESRD/transplant), and death. In the model, nonfatal cardiovascular (CV) events were included as temporary and transitional. In each study cycle, patients transitioned to new health states or remained within the same state. Transitions to the survive and DSC states might occur with or without CV events.<sup>2</sup>

The Markov model incorporated medication use and resource information directly from the IDNT and the U.S. Renal Data System (USRDS) for patients with diabetes who were receiving dialysis therapy or were post renal transplant. The cost of study drug (i.e., irbesartan 75 mg, 150 mg, 300 mg; amlodipine 2.5 mg, 5 mg, or 10 mg) was calculated by determining the exposure time by dose for all patients in the trial. Cost for each treatment dose was calculated from the average wholesale price for the year 2000. Use of concurrent antihypertensive agents by class was used to determine their contribution to bottom-line costs by treatment arm. A weighted average price in the model was assumed to be similar between treatment strategies. Mean annual costs of concurrent antihypertensives were then estimated to be \$563.44 for irbesartan, \$519.70 for amlodipine, and \$624.28 for placebo.<sup>2</sup>

The Markov model used in this study was able to predict that the use of irbesartan represents both therapeutic and economic improvement and has the potential to provide beneficial long-term clinical and cost-effective outcomes.<sup>2</sup> Table 1 summarizes the pharmacoeconomic results of the analysis. Irbesartan is cost effective compared with both amlodipine and standard antihypertensive care. At 25 years, the model predicts that the use of irbesartan increases life expectancy by 0.6 to 0.7 years (versus amlodipine and placebo, respectively) and saves \$15,607 to \$26,290 (versus placebo and amlodipine, respectively).<sup>2</sup> Figure 3 demonstrates the cumulative cost savings per 100 patients treated with irbesartan compared with amlodipine or placebo.<sup>2</sup>

A different approach was taken by the investigators involved in the RENAAL trial. Focusing on short-term savings by prolonging the time to ESRD, comparisons were made on the number of days that patients would receive ESRD therapy if they were to receive losartan versus standard antihypertensive therapy. They found that losartan reduced the number of days with ESRD by 33.6% over 3.5 years. This resulted in a savings of \$3,522 per patient over this same time period.<sup>11</sup>

Another Markov model was developed to determine the pharmacoeconomic effect of irbesartan (300 mg/day) at the earlier stage of microalbuminuria. Since irbesartan was used in both IRMA II and the IDNT, this allowed the combination of the

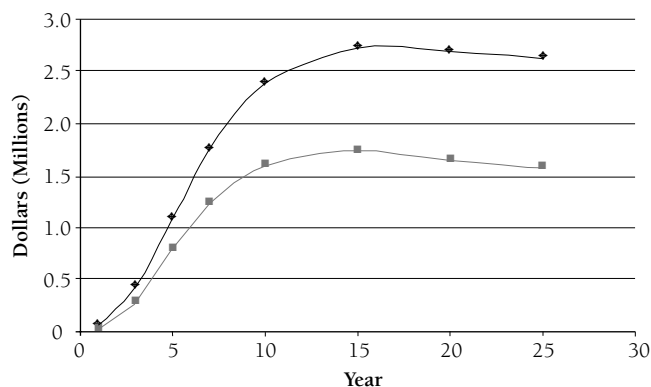
**TABLE 1** IDNT Pharmacoeconomic Results

Strategy	Savings per Patient (\$)	Mean Increase in Life Expectancy (Years)
25 years		
IRB versus AML	26,290	0.6
IRB versus PLC	15,607	0.7
10 years		
IRB versus AML	23,817	0.2
IRB versus PLC	16,026	0.3
3 years		
IRB versus AML	4,217	—
IRB versus PLC	2,778	—

IDNT = Irbesartan Diabetic Nephropathy Trial.  
 IRB = irbesartan; AML = amlodipine, PLC = placebo.  
 Adapted from Rodby et al. *Clin Ther.* 2003;25:2102-19.<sup>2</sup>

**FIGURE 3** IDNT Pharmacoeconomic Results

Cumulative Cost Savings per 100 Patients Treated With Irbesartan Over Amlodipine or Placebo Over Model Time Horizon



◆ Cost Savings (A-I)    ■ Cost Savings (P-I)  
 IDNT = Irbesartan Diabetic Nephropathy Trial.  
 Adapted from Rodby RA et al. *Clin Ther.* 2003; 25:2102-19.<sup>2</sup>

data from these 2 clinical trials to develop a Markov model that projected outcome from microalbuminuria to ESRD. This model was also designed to determine the most cost-effective time to start irbesartan—at the microalbuminuric stage as was studied in IRMA II or at the overt stage as was studied in the IDNT.<sup>12</sup> Composite end points of the clinical trial included DSC, ESRD, and death.<sup>12</sup> Three treatment strategies were compared: early use of irbesartan (with therapy initiated when microalbuminuria was detected), late use of irbesartan (treatment started when nephropathy developed), and standard antihypertensive therapy with comparable BP control.<sup>12</sup> Data were taken from IRMA II and the IDNT;<sup>12</sup> costs for ESRD and outcomes were obtained from the USRDS.<sup>12</sup> Costs and

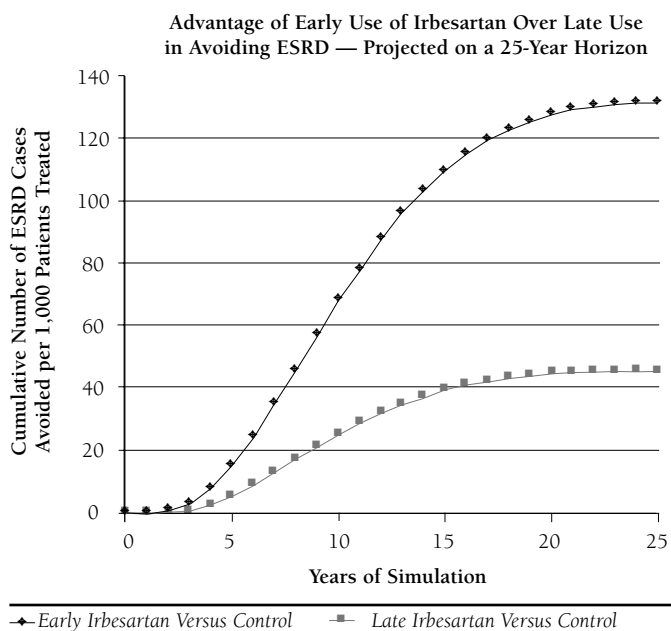
**TABLE 2** IDNT Clinical and Pharmacoeconomic Results

	Years Free of ESRD*	Cumulative Incidence ESRD (%)	LE (Years)*	LYG Versus Control (Years)*	LYG Early Versus Late Irbesartan (Years)*	25-Year Costs (\$)*	Cost Savings Versus Control (\$)*	Cost Savings Early Versus Late Irbesartan (\$)*
Control	12.4	20.0	13.19 (10.50)	–	–	28,782	–	–
Early Irbesartan	14.4	7.0	14.75 (11.46)	1.55 (0.96)	1.48 (0.92)	16,859	11,922	8,670
Late Irbesartan	12.7	16.0	13.27 (10.54)	0.07 (0.05)	–	25,529	3,252	–

\* = mean count per patient; BP = blood pressure; LE = life expectancy; LYG = life-years gained; Control = standard antihypertensive medications excluding ACE inhibitors, other angiotensin II-receptor antagonists, and dihydropyridine calcium channel blockers with equivalent blood pressure control.

Adapted from Palmer AJ et al. *Diabetes Care*. 2004;8:1897-903.<sup>12</sup>

**FIGURE 4** Pharmacoeconomic Results



Adapted from Palmer AJ. *Diabetes Care*. 2004;8:1897-903.<sup>12</sup>

microalbuminuria and continued on a long-term basis for optimal effect in BP reduction, reduction of protein excretion, and progression to ESRD and overt nephropathy.<sup>12</sup> Table 2 summarizes the clinical and pharmacoeconomic results of the trial.<sup>12</sup> Figure 4 demonstrates the advantage of early use of irbesartan over late use in avoiding ESRD over a projected 25-year period.<sup>12</sup>

### Conclusion

In 2001, data from the results of 2 trials showed the progression of kidney disease in patients with type 2 DM was slowed significantly. The IDNT demonstrated that the ARB significantly slowed the progression of ESRD to overt nephropathy. The IRMA II trial showed that using the ARB in the earlier microalbuminuric stage prevented progression to overt nephropathy. Those results allowed the creation and execution of pharmacoeconomic models to determine the financial impact of the use of irbesartan at various stages of DN. A Markov model was created for irbesartan use at the microalbuminuric and overt nephropathic stages. The model demonstrated that the use of irbesartan increased mean life expectancy from months to years, depending on when therapy was initiated in the course of the disease. In addition, irbesartan therapy resulted in mean cost savings of \$3,000 to \$12,000 per patient. These models clearly predict that the most effective strategy is to start irbesartan early, at the microalbuminuric stage.

### DISCLOSURES

This article is based on the proceedings of a satellite symposium held March 31, 2004, at the Academy of Managed Care Pharmacy's 16th Annual Meeting and Showcase in San Francisco, California, which was funded by an unrestricted educational grant from Bristol-Myers Squibb Company and Sanofi-Synthelabo Inc. partnership. Author Roger A. Rodby received an honorarium from Bristol-Myers Squibb Company and Sanofi-Synthelabo Inc. partnership for participation in the symposium upon which this article is based; he discloses that he is a consultant to Bristol-Myers Squibb Company and Sanofi-Synthelabo Inc.

life years saved were projected for a hypothetical cohort of 1,000 patients with type 2 DM. A 25-year horizon and third-party payer perspective were utilized.<sup>12</sup>

This study demonstrated that, when compared with standard antihypertensive therapy, early use of irbesartan per 1,000 patients was projected to save \$11.9 ± 3 million, and late use of irbesartan was projected to save \$3.3 ± \$2.7 million. The study also estimated that the early use of irbesartan would add 1,550 ± 270 cumulative life years per 1,000 patients, while late use added only 71 ± 40 cumulative life years. The investigators concluded that the model predicts that irbesartan should be started at the onset of

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# Emerging Trends for Prevention and Treatment of Diabetic Nephropathy: Blockade of the RAAS and BP Control

LAWRENCE G. HUNSICKER, MD

## ABSTRACT

**BACKGROUND:** Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD), and it affects 30% of patients with type 1 diabetes mellitus (DM) and 20% of patients with type 2 DM. Clinical features in both types of DM are similar and are characterized by an underlying abnormality of the microcirculation, manifested by both retinopathy and nephropathy. Clinical hallmarks of DN include elevated blood pressure (BP) and elevated urinary protein excretion. Treatment consists of maintaining BP at <130/85 mm Hg in patients without proteinuria and <125/75 mm Hg in patients with microalbuminuria or overt DN. In addition, agents that inhibit the renin-angiotensin-aldosterone system (RAAS) have been found to be effective in reducing the risk of progression to DN, a result independent of their antihypertensive effect.

**SUMMARY:** The earlier Collaborative Study Group (CGS) trial demonstrated that the angiotensin-converting enzyme (ACE) inhibitor captopril lowered BP and provided renal protection in type 1 diabetic kidney disease beyond that attributable to the BP change. The Irbesartan Diabetic Nephropathy Trial (IDNT) studied the effect of the angiotensin receptor blocker (ARB) irbesartan on the reduction of BP, urinary protein excretion, and progression to DN. The study end points in the IDNT demonstrated that ARB therapy reduced BP, reduced urinary protein excretion, and provided renal protection against progression to DN. The Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) trial demonstrated that the ARB losartan, when combined with conventional antihypertensive agents, decreased urinary protein excretion by 35%. Losartan both lowered BP and provided renal protection against DN. In a study comparing an ACE inhibitor (trandolapril), an ARB (losartan), and a combination of the 2 agents (trandolapril and losartan), data showed that all 3 arms reduced BP to the same degree. However, a combination of the ARB plus the ACE inhibitor produced both a significant reduction in urinary protein excretion beyond that seen with either agent alone and a significantly greater protection against progression to doubling of serum creatinine or ESRD. The reduction in urinary protein excretion and renal progression seen with individual agents were not statistically different from each other.

**CONCLUSION:** These studies demonstrated that the combination blockade of the RAAS axis with an ARB plus an ACE inhibitor may play an important role in the prevention and treatment of DN and may turn the tide of increasing kidney disease due to DM, improve the overall quality of life of patients with DM, and save the lives of patients with either type 1 or type 2 DM.

**KEYWORDS:** Diabetic nephropathy, Glomerulosclerosis, Kimmelsteil-Wilson lesion, Microalbuminuria, End-stage renal disease (ESRD), RAAS axis, Angiotensin receptor blocker (ARB), Angiotensin-converting enzyme (ACE) inhibitor, CGS trial, IDNT, RENAAL trial

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Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) in developed countries. In 2001, this disorder accounted for 45% of the new cases of ESRD in the United States.<sup>1</sup> Type 1 diabetes mellitus (DM) affects 0.5% of the general population. Type 2 DM is recognized in at least 4% of the population. About one third of patients with type 1 DM and approximately 20% of patients with type 2 DM have diabetic nephropathy (DN). Because of the greater worldwide prevalence of type 2 DM, which accounts for 90% of all cases, most patients with DM and ESRD have type 2 disease. There are several risk factors involved in the etiology of DN, including glomerular hypertension and hyperfiltration, systemic hypertension, hyperglycemia, and, potentially, cigarette smoking, hyperlipidemia, and gene polymorphisms that affect the renin-angiotensin-aldosterone system (RAAS). ESRD from diabetic nephropathy is more prevalent in African Americans with type 2 DM than in whites (4:1 ratio), while the reverse is true for type 1 DM.<sup>2</sup>

## Pathophysiology of Diabetic Nephropathy

The clinical features of DN in both type 1 and type 2 DM are similar, although the time from onset of recognized DM to diabetic kidney disease may be shorter in type 2 DM.<sup>2</sup> In type 2 DM, advanced pathologic changes of the kidney may be found at the time of diagnosis of DM.<sup>3</sup> There is an underlying and generalized abnormality of the microcirculation in both types of DM. In particular, the degree of retinopathy (as observed with the ophthalmoscope) can be directly correlated with the degree of renal abnormality (as indicated by proteinuria and renal biopsy). Diabetic kidney disease is characterized pathophysiologically by increased permeability of the glomerular capillary wall to protein leading to clinical proteinuria, with an associated thickening of the basement membrane and abnormalities of the glomerular arterioles. Glycosylation of many proteins occurs with DM, particularly in the collagen of the basement membrane.<sup>4</sup>

DN is generally diagnosed based on clinical grounds without a renal biopsy. Important clues to the early diagnosis, in addition to the presence of clinical DM itself, include the presence of normal-sized or enlarged kidneys, evidence of proliferative diabetic retinopathy, and microalbuminuria or overt albuminuria. Retinopathy is found in 90% of type 1 DM cases and in 60% of patients with type 2 DM who eventually develop nephropathy.<sup>2</sup>

Early abnormal microscopic changes in DN include a thickening of the glomerular basement membrane (GBM) and the expansion of the mesangium due to the accumulation of extracellular matrix. Prominent areas of nodular matrix expansion (Kimmelsteil-Wilson lesions) are seen in microscopic sections along with the thickened GBM. Laminated and

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eosinophilic nodules may be seen in the periphery of the glomeruli. In both type 1 and type 2 DM, fibrin caps, capsular drops, and gross hyalinization of the arterioles may be present.<sup>3</sup> Progressive expansion of the mesangium results in the progressive occlusion of the glomerular capillaries, ultimately producing a large acellular mass.<sup>4</sup> Over time, the mesangial matrix becomes diffusely expanded, and the glomerulus becomes sclerotic.<sup>2</sup>

The best treatment for DN is prevention. A comprehensive program of diabetic care should include early detection so that therapies can be initiated effectively.<sup>3</sup> Therapy is aimed at preventing the onset and slowing the progression of DN by controlling blood sugar and systemic blood pressure (BP), and by blockade of the RAAS. Control of glucose levels can be achieved through regulating diet and administering oral hypoglycemic agents and insulin.<sup>2</sup> In addition, a consensus panel of the American Diabetes Association has recommended protein intake reductions in patients with DM with microalbuminuria (0.8 g/kg/day is the Adult Recommended Daily Allowance and about 10% of the daily caloric intake). There is some evidence that protein intake should be restricted to 0.6 g/kg/day in patients with overt DN.<sup>5</sup>

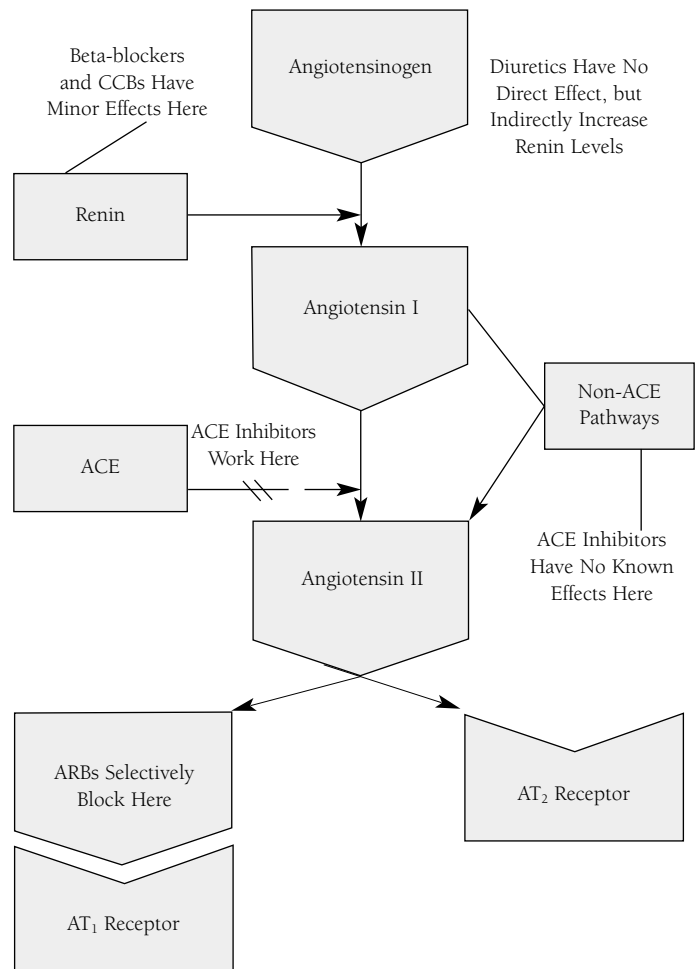
### ■ Treatment of Hypertension Associated With Diabetic Nephropathy

The development of hypertension in both type 1 and type 2 DM is a clinical hallmark. Thirty percent of patients with type 2 DM have high blood pressure when they are diagnosed, and about 70% of these patients have hypertension when nephropathy develops. The added problems associated with renal vascular disease contribute to hypertension in about 20% of all patients with type 2 DM and in almost 40% of those patients with overt nephropathy.<sup>6</sup>

Numerous clinical studies in both types of DM have demonstrated the value of strict BP control in reducing albumin excretion and in inhibiting the decline in renal function. In order to preserve renal function, BP should be maintained at <130/85 mm Hg in patients with DM without proteinuria. When patients have shown evidence of microalbuminuria or nephropathy, a slightly lower target blood pressure (125/75 mm Hg) is advised.<sup>5</sup>

Agents blocking the RAAS (angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]) reduce the progression of overt nephropathy in both type 1 and type 2 DM—both through BP reduction and through mechanisms independent of BP—and should be initiated whenever microalbuminuria or overt proteinuria is detected. Figure 1 shows the role of ACE inhibitors and ARBs in RAAS blockade. If use of an ACE inhibitor produces unmanageable side effects (e.g., allergy, cough, or angioedema), an ARB can be used as an alternative agent, and vice versa. ACE inhibitors and ARBs are the only agents shown to produce a drug-specific benefit in DN independent of BP control.<sup>5</sup>

**FIGURE 1** Renin-Angiotensin-Aldosterone System



ACE = angiotensin-converting enzyme; CCBs = calcium channel blockers; ARBs = angiotensin receptor blockers; AT = angiotensin.

### ■ Summary

#### Treatment of Patients With Microalbuminuria

The DM substudy of the Heart Outcomes Prevention Evaluation (HOPE) clinical trial examined patients with type 2 DM and microalbuminuria and demonstrated that treatment with an ACE inhibitor provided a 24% reduction in the rate of progression to overt nephropathy compared with the group receiving placebo, despite similar BPs in both groups.<sup>6</sup> In the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA II) trial, treatment with irbesartan (300 mg/day) decreased the level of urinary albumin secretion by 38% from baseline. Over a 3-year follow-up period, irbesartan also reduced the risk of progression to macroalbuminuria by 70% compared with placebo.<sup>6,7</sup> Irbesartan was less effective when used at the dose of 150 mg/day.<sup>7</sup> Other

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clinical trials of patients with type 2 DM and overt nephropathy demonstrated that ACE inhibitors were more effective than other antihypertensive agents in reducing proteinuria. (ARBs were not included in these studies.)<sup>6</sup>

### Treatment of Patients With Overt Proteinuria

In an earlier randomized controlled trial conducted by the Collaborative Study Group (CSG), the ACE inhibitor captopril was shown to protect against deterioration of renal function in patients with type 1 DM and nephropathy and to be significantly more effective than BP control alone.<sup>8</sup> In this trial, 207 patients received captopril and 202 received placebo. Inclusion criteria for all patients consisted of type 1 DM with urinary protein excretion >500 mg/day and a serum creatinine concentration of <2.5 mg/dL (220  $\mu$ mol/L). The goal for BP control was the same (<140/90 mm Hg) in both groups, with BP control achieved using adjunctive agents other than ACE inhibitors. Median follow-up was 3 years. The primary end point was a doubling of the baseline serum creatinine concentration.<sup>8</sup>

The CSG investigators' research supported the proposal that captopril beneficially alters glomerular hemodynamics in patients with DM by a mechanism independent of its antihypertensive properties.<sup>8</sup> ACE inhibitors are known to decrease urinary protein excretion in patients with type 2 DM and other glomerulopathies. In this study, use of captopril also resulted in decreased proteinuria. The beneficial effects of captopril on glomerular hemodynamics and on glomerular pathology were suggested to explain the decrease in proteinuria.<sup>8</sup>

### The Irbesartan Diabetic Nephropathy Trial

The CSG investigators designed the Irbesartan Diabetic Nephropathy Trial (IDNT) to determine whether the use of an ARB or a calcium channel blocker (CCB) would provide protection against the progression of nephropathy due to type 2 DM beyond the agents' known antihypertensive effects.<sup>9</sup>

In the IDNT, 1,715 hypertensive patients with nephropathy due to type 2 DM were randomly assigned to 3 treatment arms: (1) irbesartan 300 mg daily, (2) amlodipine 20 mg daily, or (3) placebo. The target BP was 135/85 mm Hg or less in all groups, again with control being achieved with the use of adjunctive antihypertensive agents other than ACE inhibitors, ARBs, or CCBs.<sup>9</sup> The 3 groups were compared with regard to the time to the primary composite end point of a doubling of baseline serum creatinine concentration, the development of ESRD, or death from any cause. All groups were also compared with a secondary cardiovascular end point. The IDNT mean duration of follow-up was 2.6 years.<sup>9</sup>

The investigators found that therapy with irbesartan resulted in a 20% lower risk of the primary end point compared with the placebo group ( $P = 0.02$ ) and a 23% lower risk than the amlodipine group ( $P = 0.006$ ). The risk of doubling the serum creatinine concentration was 33% lower in the irbesartan group

compared with the placebo group ( $P = 0.003$ ) and 37% lower in the irbesartan group compared with the amlodipine group ( $P < 0.001$ ).<sup>9</sup>

Data from this trial showed that treatment with irbesartan was associated with better renal outcomes than the other study agents (i.e., amlodipine and placebo). Use of the ARB agent produced a reduction in the rate of progression of the nephropathy, which was reflected in a significant increase in the time to a doubling of the serum creatinine concentration (representing an approximate halving of the glomerular filtration rate [GFR]). At 3 years of follow-up, the absolute reduction in the rate of doubling of serum creatinine was 11.5% (from 27.2% in patients receiving placebo to 15.7% in patients receiving irbesartan). Thus, one prevents 1 patient from doubling by treating 9 patients with irbesartan for a period of 3 years.<sup>9</sup> The mean rate of increase in the serum creatinine concentration and the mean rate of decrease in creatinine clearance were significantly lower in the group of patients receiving irbesartan.<sup>9</sup> The investigators interpreted these results as demonstrating that irbesartan was renoprotective in patients with nephropathy due to type 2 DM.<sup>9</sup> The renoprotective effects were similar to those described previously,<sup>8</sup> when the ACE inhibitor captopril was used in patients with nephropathy due to type 1 DM.<sup>9</sup>

The effect of baseline proteinuria and change in proteinuria was also investigated in the IDNT in patients with DN. Proteinuria has been shown to have a strong correlation with the rate of renal disease progression. In an analysis involving 1,608 patients with baseline 24-h proteinuria, urine protein was seen as a significant predictor of poor outcome with a relative risk (RR) for renal disease of 2.06 for each doubling of proteinuria ( $P < 0.0001$ ). Among 1,261 patients with proteinuria at baseline and at 12 months follow-up, the reduction of urine protein at 12 months was associated with a significant reduction of the risk of renal end point (RR = 0.52) for each halving of the proteinuria value ( $P < 0.0001$ ). The investigators observed that proteinuria was reduced significantly more in those patients who received irbesartan than in those who received either amlodipine or placebo. The beneficial results of irbesartan as protection against the progression of renal failure in DN were found to be strongly correlated with the reduction in proteinuria.<sup>10</sup>

### Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) Study

The Reduction of End Points in Non-Insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) Study compared losartan with conventional antihypertensive therapy (without ACE inhibitors). This study found that losartan, when combined with conventional antihypertensive treatment, decreased the level of urinary protein excretion by 35% and reduced the risk of ESRD by 28%.<sup>11</sup>

In the RENAAL study, the primary composite end point of a doubling of the serum creatinine concentration, ESRD, or death was reached in 327 patients (43.5%) compared with 359 patients



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enrolled in the placebo arm (47.1%). The investigators concluded that therapy with losartan produced a statistically significant 16% reduction in the risk of the primary composite end point ( $P = 0.02$ ).<sup>11</sup> The risk of doubling the serum creatinine concentration was 25% lower in the losartan group than in the placebo arm of the trial ( $P = 0.006$ ). The study found no significant difference in mortality between the 2 groups ( $P = 0.88$ ), but the risk of the combined end point (i.e., ESRD or death) was 20% lower in the losartan group compared with patients who received placebo.<sup>11</sup> The investigators concluded that losartan, combined with conventional antihypertensive agents as required, provided strong renal protection and reduced BP in patients with type 2 DM and nephropathy.<sup>11</sup> The primary benefit attained from the administration of losartan was a significant improvement in renal outcomes in addition to the effects of its antihypertensive properties in patients with type 2 DM and nephropathy.<sup>11</sup> Table 1 summarizes and compares the results and end points of the IDNT and the RENAAL study.

**Angiotensin-converting Enzyme Inhibitor Plus  
Angiotensin Receptor Blocker Therapy in Renal Disease**

A double-blind, randomized clinical trial was conducted to assess the effectiveness and safety of combined therapy with ACE inhibitors plus ARBs compared with monotherapy with each agent at maximum dosage in patients with nondiabetic renal disease.<sup>12</sup>

Study enrollment in the Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-converting Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) trial consisted of 336 patients with nondiabetic renal disease (primarily IgA nephropathy). The patients were screened, and after an 18-week run-in period, 263 were randomly assigned to an ARB (losartan 100 mg daily), an ACE inhibitor (trandolapril 3 mg daily), or a combination of the drugs at equivalent doses. The 3 arms of the trial were compared using survival analysis on the combined end point of time to doubling of serum creatinine concentration or ESRD. Analysis was performed on an intention-to-treat basis.<sup>12</sup> Inclusion criteria for the study were: 18 to 70 years of age, chronic nephropathy with serum creatinine of 133 to 398  $\mu\text{mol/L}$ , GFR of 20 to 70 mL/min per 1.73  $\text{m}^2$  (with variation of <30% in at least 3 consecutive measurements), diagnosed nondiabetic renal disease, and persistent proteinuria with urinary protein excretion >0.3 g/day (for at least 3 months with no evidence of overt heart failure or urinary tract infection).<sup>12</sup>

Achieved BPs in the 3 arms of the study were identical. Mean systolic and diastolic BP of all study subjects was reduced by antihypertensive agents to a mean of 128/80 mm Hg after randomization.<sup>12</sup> When compared with baseline values, the mean systolic BP fell by 5.2 mm Hg in the trandolapril group, 5.3 mm Hg in the combination therapy group, and 5.1 mm Hg in the losartan group. Mean diastolic BP was reduced by 2.9 mm Hg in the trandolapril arm, 3.0 mm Hg in the combination therapy arm, and 2.9 mm Hg in the losartan arm. There was no statistically

**TABLE 1** Comparison of Major End Points of RENAAL and IDNT Trials

Study End Points	RENAAL <sup>11</sup>	IDNT <sup>9</sup>		
	Mean Follow-up: 3.4 years	Mean Follow-up: 2.6 years		
	Losartan Versus Control	Irbesartan Versus Control	Irbesartan Versus Amlodipine	Amlodipine Versus Control
	% RRR	% RRR	% RRR	% RRR
Doubling of creatinine, ESRD*, or death	16 ( $P = 0.02$ )	20 ( $P = 0.02$ )	23 ( $P = 0.006$ )	-4 ( $P = 0.69$ )
Doubling of creatinine	25 ( $P = 0.006$ )	33 ( $P = 0.03$ )	37 ( $P < 0.001$ )	6 ( $P = 0.60$ )
ESRD	28 ( $P = 0.002$ )	23 ( $P = 0.07$ )	23 ( $P = 0.07$ )	0 ( $P = 0.99$ )
Death	-2 ( $P = 0.88$ )	8 ( $P = 0.57$ )	-4 ( $P = 0.80$ )	12 ( $P = 0.40$ )
CV mortality and mortality	10 ( $P = 0.26$ )	9 ( $P = 0.40$ )	-3 ( $P = 0.79$ )	12 ( $P = 0.29$ )

\* ESRD = end-stage renal disease. The RENAAL trial defined ESRD as the need for long-term dialysis or transplantation. The IDNT defined ESRD as being indicated by the initiation of dialysis, renal transplantation, or a serum creatinine concentration of at least 6.0 mg/dL.

RRR = relative risk reduction; RENAAL = Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan trial; IDNT = Irbesartan Diabetic Nephropathy Trial; CV = cardiovascular.

Lewis EJ et al. *N Engl J Med.* 2001;345:851-60.<sup>9</sup>

Brenner BM et al. *N Engl J Med.* 2001;345:861-69.<sup>11</sup>

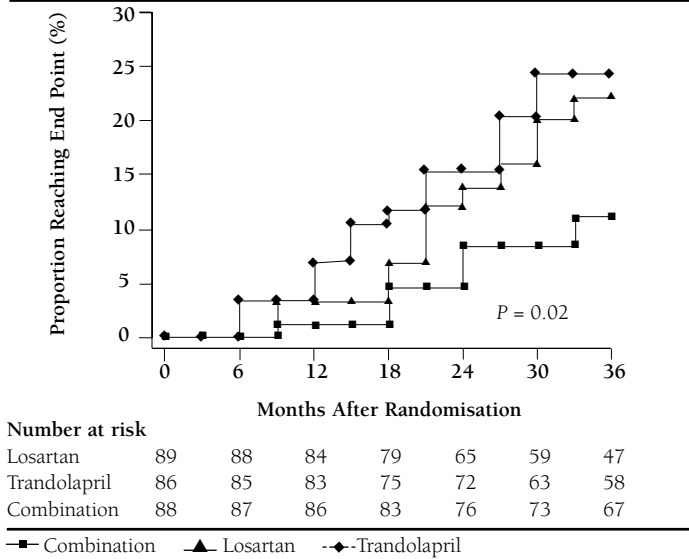
significant difference in BP reduction among the 3 study groups ( $P = 0.109$ ).<sup>12</sup>

Despite the similarity of achieved BPs, the investigators found that 11% (10 of 85) receiving combination therapy (losartan and trandolapril) reached the primary end point, compared with 23% (20 of 85) who received trandolapril monotherapy ( $P = 0.018$ ). Twenty-three percent (20 of 86) of patients receiving losartan monotherapy reached the combined primary end point ( $P = 0.016$ ).<sup>12</sup> Figure 2 shows the percentages of patients by treatment group who reached end point. A distinct benefit of combination therapy was observed in the retardation of progression of renal disease for patients with high rates of urinary protein excretion and for those with small amounts of proteinuria.<sup>12</sup>

The rate of urinary protein excretion was significantly reduced in all 3 treatment groups, and the reduction rate was greatest in the combination treatment group ( $P = 0.01$ ). The greatest median change in daily urinary protein excretion was -42.1% in the losartan group, -44.3% in the trandolapril group, and -75.6% in the combination group. Patients with severe proteinuria (>3 g/day) in the combination group demonstrated a greater reduction after treatment than did patients with less severe proteinuria (<1 g/day). Comparison of the 3 treatment groups in terms of reducing

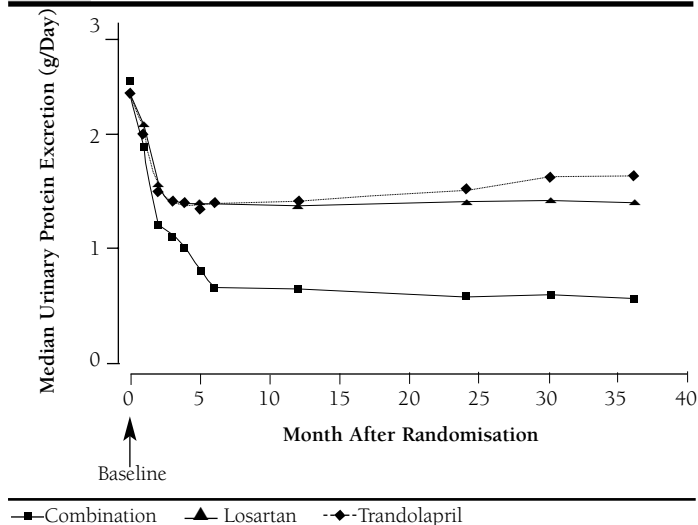
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**FIGURE 2** Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-converting Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) Trial—Percentages of Patients Reaching End Point by Treatment Group



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**FIGURE 3** Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-converting Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE) Trial—Median Urinary Protein Excretion by Treatment Group



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urinary protein excretion showed that combination therapy was superior to either monotherapy at any range (including <1 g/day). Once maximum antiproteinuric effects had been achieved in the combination group and the losartan group, proteinuria remained constant for the duration of the trial period.<sup>12</sup> Figure 3 shows the median urinary protein excretion by treatment group.<sup>12</sup>

Combination therapy was shown to be significantly better than therapy with the individual agents in renal survival of nondiabetic patients who have moderately reduced renal function and moderate daily protein excretion.<sup>12</sup> The most important difference among the treatment groups appeared to be attributable to the significant antiproteinuric effect of combination therapy. The investigators found that the 3-year renal survival rate in the combination-therapy arm was mainly attributable to that result. The significant antiproteinuric effect (as shown in Figure 3) was demonstrated irrespective of baseline proteinuria and level of renal dysfunction. Moreover, the greater the baseline proteinuria, the more significant the reduction in urinary protein excretion. Reductions in urinary protein were noticed in the monotherapy groups, but combination treatment further reduced proteinuria over any range of the baseline proteinuria and renal dysfunction variables.<sup>12</sup> The study results indicated that combination therapy was well tolerated even in patients with advanced renal insufficiency. The data also support the theory that the RAAS plays a part in the progression of renal disease. Lastly, the trial results indicated that combination ARB/ACE inhibitor therapy may produce different efficacy in various subtypes of renal disease.<sup>12</sup>

**Conclusion**

The IDNT and RENAAL studies confirm the efficacy of ARBs in slowing the progression of established renal disease in patients with type 2 DM. These studies also provide an opportunity to estimate the optimal targets for BP control in these patients and to determine whether blockade of the RAAS is equally important at all achieved levels of BP control. In the IDNT, a direct correlation was shown between follow-up systolic BP and the risk of an adverse renal outcome (with no lower limit to this relationship). Once the impact of follow-up systolic BP is accounted for, diastolic BP and baseline systolic BP are unrelated to renal outcomes. It appears that the optimal systolic BP goal lies between 120 mm Hg and 130 mm Hg. Importantly, the IDNT analyses also show that RAAS blockade is equally important at all levels of achieved systolic BP, even at the lowest achieved levels. The effect of systolic BP control and RAAS blockade are independent and additive. Irbesartan-treated patients whose BP was reduced by 20 mm Hg (median achieved in the IDNT) from baseline to follow-up had a 63% reduction in risk of an adverse renal outcome. Finally, very recent data suggest that the combination of an ACE inhibitor plus an ARB offers greater protection against progression of kidney disease than either agent alone.

Other analyses of the IDNT and RENAAL study have shown that the strongest baseline predictor of a renal outcome is

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proteinuria. Additionally, reduction of proteinuria, which is associated both with ARB therapy and with BP reduction, is strongly predictive of a good outcome. This suggests that the effectiveness of the treatment can be monitored by following the levels of proteinuria. That finding is particularly important in the clinician's approach to the earliest stages of diabetic kidney disease, in which microalbuminuria is the only characteristic and in which the protection of GFR cannot be easily demonstrated within the duration of a typical clinical trial. The combination of blocking the RAAS and aggressively reducing BP provides the means for decreasing the incidence of kidney disease due to DM—thereby saving lives and improving the quality of patients' lives.

### DISCLOSURES

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# Implementing the New Guidelines for Hypertension: JNC 7, ADA, WHO-ISH

BARRY L. CARTER, PharmD, FCCP, FAHA, BCPS

## ABSTRACT

**BACKGROUND:** The new guidelines issued by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) emphasize that aggressive blood pressure (BP) control is essential to reducing morbidity and mortality. Additionally, guidelines issued by the American Diabetes Association (ADA) and the World Health Organization-International Society of Hypertension (WHO-ISH) emphasize the critical need for lowering BP levels.

Achieving BP goals is a challenge for patients and their physicians, and most patients are not at goal. Poor BP control is even more of a challenge for patients with diabetes and chronic kidney disease since their goals are even lower. The strategies for lowering BP levels include patient lifestyle changes, adherence to therapy, and regular monitoring of BP levels.

**OBJECTIVE:** To summarize the antihypertension guidelines recommended by WHO-ISH, JNC 7, the ADA, and the Hypertension in African Americans Working Group (HAAW Group) of the International Society on Hypertension in Blacks and evaluate the pharmacist's collaborative role in the management of hypertension by examining the results of programs designed to include pharmacist counseling.

**METHODS:** The relevant literature was evaluated and reviewed. Emphasis was placed on literature that evaluated strategies to improve BP control.

**RESULTS:** Results from several programs and studies showed positive effects of pharmacist collaboration. A program that provided pharmacist academic detailing to physicians at 5 Veterans Affairs facilities resulted in significant increases in patients receiving  $\beta$ -blocker therapy or thiazide diuretics and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy. Another study in which hypertensive patients received clinical services from pharmacists showed significant improvement in patients' knowledge of hypertension and its management and in patient adherence, and also showed a significant increase in the number of patients whose BP stayed in the normal range. A 6-month, controlled, single-blind, parallel-group study of 51 hypertensive patients showed significant improvements in BP control, quality of life, and overall patient satisfaction in the study group that received treatment through a primary care team that included pharmacists. Among patients at a Veterans Administration medical center, results suggested that the intervention of a clinical pharmacist improved documentation of drug therapy and estimated patient compliance. A study of the effectiveness of comanagement in 197 hypertensive patients with physician-pharmacist collaboration using an evidence-based, systematic approach showed that a significantly larger number of patients in the study group achieved BP control than in the control group.

**CONCLUSIONS:** The expanded role of clinical pharmacists in programs for evaluating, monitoring, and treating patients with hypertension can result in improved adherence to therapy and established guidelines. As members of interdisciplinary health care teams, pharmacists should utilize the JNC 7 guidelines and scientific evidence to consult with physicians about medications, design effective formulas, and collaborate with physicians in evaluating and comanaging patients with hypertension.

**KEYWORDS:** Hypertension, End-stage renal disease, WHO-ISH, JNC 7, HAAW Group, American Diabetes Association, Physician-pharmacist collaboration, Academic detailing, Clinical pharmacist, Guideline implementation, Prescribing patterns, Patient adherence

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Hypertension is a major public health problem in developed nations. It is common, asymptomatic, readily detectable, and easily treatable—and it can lead to lethal complications if not treated. In the late 1960s and the 1970s, educational programs were developed to alert the population about the dangers of hypertension. As a result of those initiatives, a significant reduction in the prevalence of undiagnosed and/or untreated patients to about 25% was seen by the late 1980s, with a corresponding decline in associated cardiovascular mortality.<sup>1</sup>

By the mid 1990s, however, the effects of educational programs began to decline. The population of undiagnosed patients with hypertension increased to nearly 33%, the decline in cardiovascular mortality plateaued, and the number of patients with chronic disease related to untreated or inadequately treated hypertension increased. Additionally, the prevalence of end-stage renal disease (ESRD) per million people increased from <100 in 1982 to >250 in 1995. Correspondingly, the prevalence of congestive heart failure in people aged 55 to 75 years more than doubled between 1976 and 1980 and 1988 and 1991. Although the pathogenesis of hypertension is now better understood, the etiology is still unknown in 90% to 95% of cases.<sup>1</sup>

## Epidemiology of Hypertension

The prevalence of hypertension is predicated on the racial composition of the demographic groups studied and upon the defining criteria. In a white suburban population such as the one used in the Framingham Study, almost 20% of people in the study have blood pressure (BP) >160/95 mm Hg and almost 50% have a BP >140/90 mm Hg. Higher prevalence rates have been documented in the nonwhite population. In the female population, the prevalence of hypertension is related to age, with a significant rise in BP after age 50 that may be related to the hormonal changes occurring with menopause. The frequency ratio of hypertension in females versus males increases from 0.6 to 0.7 at age 30 to 1.1 to 1.2 by age 65.<sup>1</sup>

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### Drug Therapy for Hypertension

There are 6 major classes of antihypertensive agents: thiazide diuretics, antiadrenergic agents, vasodilators, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). The rational use of an agent depends upon its site and mechanism of action as well as on the evidence that supports its use to decrease the rate of adverse outcomes related to hypertension.<sup>2</sup>

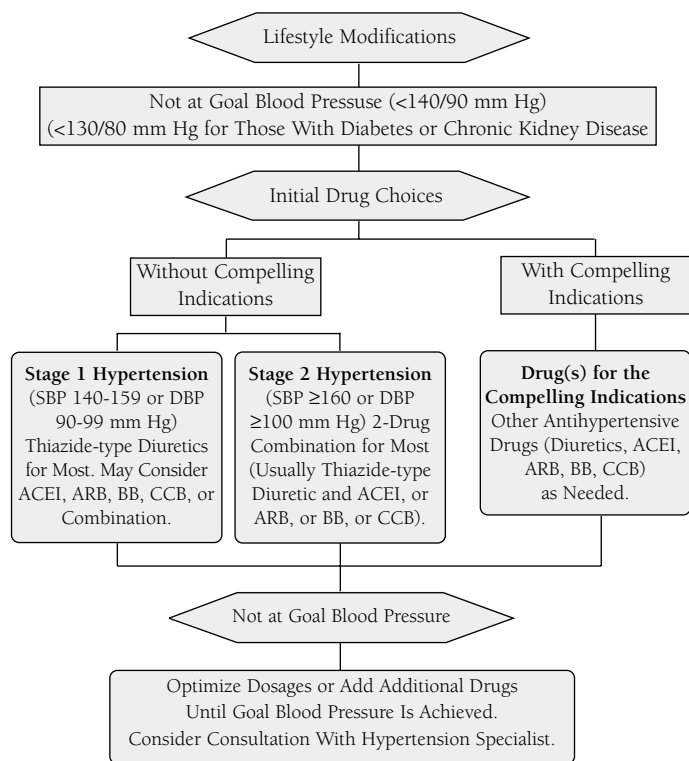
The goal of drug therapy is to use these agents alone or in combination to restore arterial pressure to normal limits in order to avoid adverse patient outcomes as a result of the hypertension, while avoiding side effects from the medication. Because the exact mechanisms underlying arterial hypertension are often not understood completely on an individual patient basis, an empirical approach is used when treating most patients. The empirical approach considers efficacy, safety, cost, impact on the patient's quality of life, ease of administration, and patient adherence. If antihypertensive agents are used in combination, they are usually chosen for their different mechanisms of action. Most patients are initially treated with a single agent, but instances of severe hypertension demonstrating an average diastolic pressure >130 mm Hg generally require intensive therapy using several agents.<sup>1,2</sup>

### Antihypertension Guidelines

Two major authoritative groups have developed treatment guidelines to follow when patients are being managed: the World Health Organization-International Society of Hypertension (WHO-ISH) and the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC). The approaches provided by these groups are similar and are based on the results of randomized clinical trials.

The Seventh Report of the JNC (JNC 7) recommends initial therapy with a diuretic for most patients with essential hypertension because diuretic agents have demonstrated a positive effect on morbidity and mortality.<sup>2</sup> WHO-ISH guidelines recommend beginning therapy with any of 6 classes of antihypertensive agents. The differences in recommendations reflect data from clinical trials that demonstrated a reduction in morbidity and mortality with long-acting CCBs versus placebo, with results similar to reports for diuretics and  $\beta$ -blockers.<sup>1</sup> The JNC 7 guidelines stress that aggressive BP control is essential to reduce morbidity and mortality.<sup>2</sup> Unfortunately, most patients are not at their BP goal. Poor BP control rates are even more of a problem for patients with diabetes (DM) and chronic kidney disease because their BP goals are even lower than for those patients with essential hypertension.<sup>2</sup> Managed care organizations will be increasingly expected to achieve high BP control rates in their members. Therefore, they must evaluate how pharmacists can be integrated in programs to achieve optimal improvement in BP control.

**FIGURE 1** JNC-7 Algorithm for Treatment of Hypertension



Reprinted with permission. Chobanian AV et al. Hypertension. 2003;42:1206-52.<sup>2</sup> SBP = systolic blood pressure; DBP = diastolic blood pressure; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CCB = calcium channel blocker.

### Objective

There are many important strategies, including interdisciplinary approaches, that can be used to implement BP guidelines. Two of the most effective strategies to achieve better adherence to BP guidelines involve physician-pharmacist collaboration or pharmacist-managed hypertension clinics. Pharmacists should use the new JNC 7 guidelines issued in May 2003 and other scientific evidence to educate prescribers, design effective formularies, and collaborate with physicians in direct management of patients with hypertension. This article will summarize the recommendations of the JNC guidelines as well as hypertension guidelines for special populations that should be promoted by pharmacists. This article will also describe how managed care pharmacists can contribute to hypertension management in a number of ways, including formulary management, academic detailing, population-based approaches to assess adherence to BP guidelines and BP control, and physician-pharmacist comanagement.

**TABLE 1** American Diabetes Association Guidelines in Hypertension Management

Target BP goal for patients with diabetes— $\leq 130/80$  mm Hg\*

Patients with systolic BP 130 to 139 mm Hg or diastolic BP 80 to 89 mm Hg

- Lifestyle/behavioral therapy for 3 months maximum
- If targets not achieved after 3 months, add pharmacologic agents that block the renin-angiotensin-aldosterone system
- Pharmacologic regimen that includes either an ACE inhibitor or ARB†
- Add a thiazide diuretic if needed to achieve BP target

\* Multiple-drug therapy (2 or more agents at proper doses) is usually required to achieve target BP. BP should be lowered gradually in elderly hypertensive patients. Patients who do not achieve target BP on 3 drugs (including a diuretic) and patients with significant renal disease should be referred to a physician experienced with patients who have hypertension.

† Clinical trials show that: (1) angiotensin-converting enzyme (ACE) inhibitors delay the progression of nephropathy in patients with type 1 diabetes mellitus (DM) who have hypertension and any degree of albuminuria, (2) ACE inhibitors and angiotensin receptor blockers (ARBs) delay the progression to macroalbuminuria in patients with type 2 DM who have hypertension and microalbuminuria, and (3) an ARB should be strongly considered for patients with type 2 DM who have hypertension and macroalbuminuria ( $>300$  mg/day).

BP = blood pressure.

Adapted from American Diabetes Association. *Diabetes Care*. 2004; 27:S65-S67.<sup>3</sup>

## Methods

### JNC 7 Goals of Antihypertensive Therapy

JNC 7 provides an evidence-based approach to the prevention and management of hypertension. In patients older than 50 years, a systolic blood pressure (SBP)  $>140$  mm Hg is a clinically more significant predictor of cardiovascular disease than the diastolic blood pressure (DBP). Starting with a BP of 115/75 mm Hg, the cardiovascular risk doubles for each increment over 20/10 mm Hg. Patients who are normotensive at age 55 can expect to have a 90% lifetime risk of developing hypertension. Patients considered to be prehypertensive (i.e., 120-139 mm Hg/80-89 mm Hg) require lifestyle modifications to prevent the progression to hypertension.<sup>2</sup>

The JNC 7 algorithm for the treatment of hypertension is presented in Figure 1.<sup>2</sup> Therapy usually begins with lifestyle modifications (i.e., diet, weight loss, and exercise regimen).<sup>2</sup> The JNC 7 recommends that initial therapy for uncomplicated hypertension consist of a thiazide diuretic alone or in combination with another agent from one of the other classes of antihypertensives (e.g., CCBs,  $\beta$ -blockers, ARBs, ACE inhibitors).<sup>2</sup> If a patient's BP is  $>20$  mm Hg above the systolic goal or  $>10$  mm Hg above the diastolic goal, initial therapy with 2 agents, either as separate prescriptions or in fixed-dose combinations, should be considered.<sup>2</sup> When patients have DM or chronic kidney disease, 2 or more antihypertensive agents will be needed to

achieve BP goals of  $<130/80$  mm Hg. Patient adherence to therapy is considered an important factor in the overall treatment of all hypertensive patients.<sup>2</sup>

Initial therapy with more than one agent greatly increases the chances of reducing BP quickly. The advantage of multiple-agent therapy to treat hypertension is that combinations often produce greater BP reductions at lower doses and produce fewer adverse events. Use of generic drugs should be considered to reduce prescription costs. The cost of separate prescriptions for multiple generic agents may be less than for a nongeneric, fixed-dose combination drug. Beginning therapy with multiple agents, however, may increase the risk of hypotension, particularly in some older patients and in patients with DM and autonomic dysfunction.<sup>2</sup>

### Blood Pressure Control in Special Populations

The strategies suggested in the JNC 7 are appropriate for the empiric management of most patients with essential hypertension. Therapy of special populations with hypertension may present particular challenges and require special attention in order to reduce hypertension-related morbidity and mortality in these vulnerable groups. Adequate BP control is difficult to achieve in special populations, particularly in African Americans and patients with DM.<sup>3,4</sup>

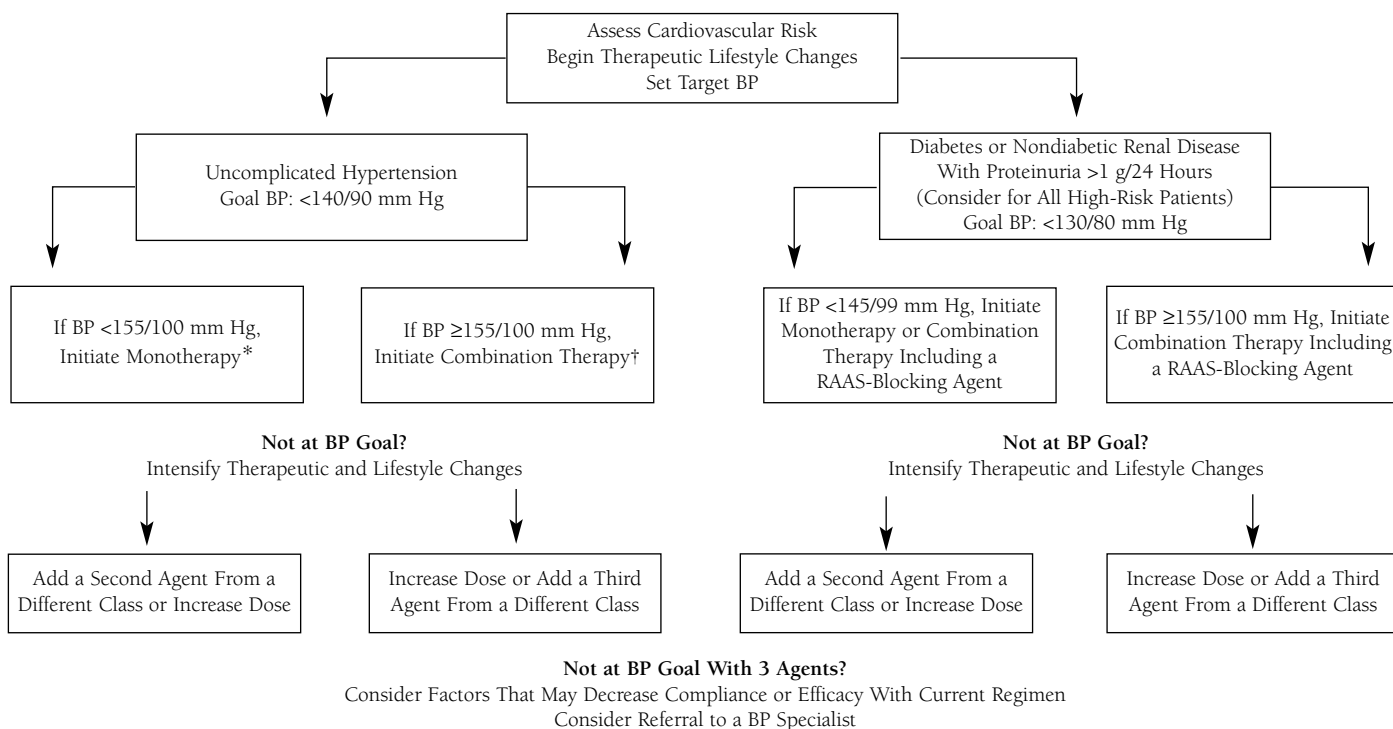
### Patients With Diabetes

Hypertension ( $>130/80$  mm Hg) is a common comorbid condition in  $\sim 20\%$  to  $60\%$  of all patients with DM and is often combined with factors such as obesity, ethnicity, and age. In type 2 DM, hypertension is frequently present as part of the metabolic syndrome of insulin resistance, which also includes central obesity and dyslipidemia. In type 1 DM, hypertension may be the harbinger of diabetic nephropathy. Elevated BP also increases the risk of both macrovascular and microvascular complications such as neuropathy, nephropathy, retinopathy, peripheral vascular disease, coronary heart disease, and stroke.<sup>5</sup> Hypertension in patients with DM is often a consequence of renal disease, which can be coincidental or part of the early malnutrition adaptation syndrome. Clinicians are undecided as to whether hypertension or renal disease comes first in patients with DM. In type 1 DM, the presence of microalbuminuria points to mild renal involvement. In type 2 DM, hypertension and microalbuminuria appear to develop in parallel.<sup>4</sup> Treatment guidelines recommended by the American Diabetes Association (ADA) are summarized in Table 1 and include lower BP targets for patients with DM (goal is  $<130/80$  mm Hg) as well as ACE inhibitors or ARBs as cornerstones in the therapy of patients with DM and hypertension.<sup>3</sup>

### African American Patients

In addition to a higher prevalence of hypertension, African Americans also have much higher rates of cardiovascular mortality, hypertension-related heart disease, congestive heart

**FIGURE 2** Clinical Algorithm for Achieving Target Blood Pressure (BP) in African American Patients With High BP



\* Initiate monotherapy at the recommended starting dose with an agent from any of the following classes: diuretics,  $\beta$ -blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARBs).

† Initiate low-dose combination therapy with any of the following combinations:  $\beta$ -blocker/diuretic, ACE inhibitor/diuretic, ACE inhibitor/CCB, or ARB/diuretic.

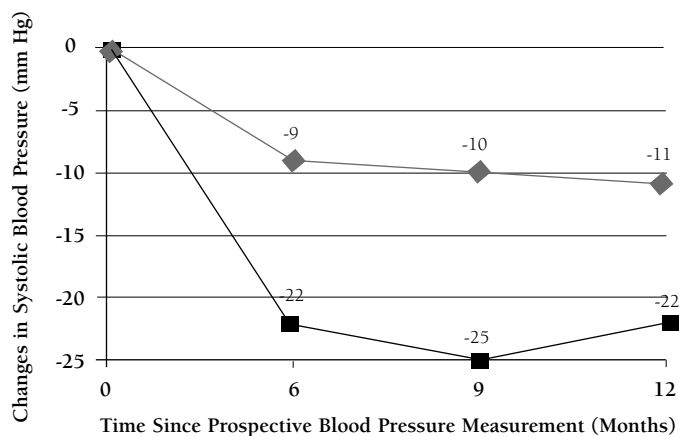
RAAS = renin-angiotensin-aldosterone system.

Douglas JG et al. Arch Intern Med. 2003;163-525-41. Copyright© 2003, American Medical Association. All rights reserved.<sup>6</sup>

failure, stroke, type 2 DM, hypertensive nephropathy, and ESRD.<sup>6</sup> Early diagnosis and persistent treatment of hypertension are required to address the resulting enormous burden of disease for African Americans.<sup>6</sup> Treatment recommendations for this population are based on the results of clinical studies, a synthesis of existing guidelines, pharmacologic options, and a consensus of the opinions of the Hypertension in African Americans Working Group (HAAW Group) of the International Society on Hypertension in Blacks. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALL-HAT), in which 36% of the participants were African American, evaluated antihypertensive agents and lipid-lowering agents. The African American Study of Kidney Disease and Hypertension (AASK) also contributed to treatment guidelines. In addition, 2 major hypertension management guidelines—JNC 7 and WHO-ISH—were considered for their relevance in the management of hypertension in African Americans.<sup>6</sup> Figure 2 summarizes the recommendations for the treatment of hypertension in African Americans.<sup>6</sup>

Because African Americans carry a larger burden of risk for cardiovascular disease, it is imperative that they achieve adequate BP goals. Patients with type 2 DM (with or without nephropathy) or with nondiabetic renal disease with proteinuria characterized by >1 g/day should have a BP target goal of <130/80 mm Hg.<sup>6</sup> Most African Americans will require combination therapy to reach target BP levels. When 2 agents are used, the following combinations may be considered particularly effective:  $\beta$ -blocker/diuretic, ACE inhibitor/diuretic, ACE inhibitor/CCB, or ARB/diuretic. New data suggest that thiazide diuretics,  $\beta$ -blockers, renin-angiotensin-aldosterone system (RAAS) blocking agents, and dihydropyridine CCBs reduce the risk of end-organ damage and poor outcomes. When there is a compelling indication to use a specific agent (e.g.,  $\beta$ -blocker following myocardial infarction), race should not influence that decision. If the patient's BP cannot be controlled with such a medication, the addition of a thiazide diuretic will frequently overcome any racial differences in antihypertensive response.<sup>6</sup>

**FIGURE 3** Significant Reductions in Systolic Blood Pressure Over 12 Months With Physician-Pharmacist Comanagement



Usual Care (UC) (◆ 99 patients) versus the physician-pharmacist comanagement (PPCM) (■ 98 patients). The mean reduction in SBP was greater in PPCM than UC patients at 6, 9, and 12 months ( $P < 0.01$  for all comparisons).

Reprinted with permission. Borenstein JE et al. *Pharmacotherapy*. 2003;23:209-16.<sup>8</sup>

### The Pharmacist's Collaborative Role in the Management of Hypertension

Achieving BP goals begins with making lifestyle changes. At the outset, the physician and patient must agree on BP goals and the estimated time to reach those goals. That information should be recorded in the patient's chart and discussed at each evaluation. Patients must be educated to accept that making lifestyle changes is essential to BP reduction. The role of the pharmacist in helping to achieve patient adherence has become a crucial component of the behavioral change necessary to achieve healthy BP goals.<sup>2</sup>

The pharmacist's unique position in the health care system provides a vantage point from which to assist with solving medication-related problems. Moreover, studies have demonstrated that when pharmacists are integrated into the hypertension management team, the control rates for BP improve and drug interactions, patient nonadherence, and costs decrease.<sup>7</sup>

### Pharmacist-Physician Collaborative Models in the Treatment of Hypertension

Collaborative relationships between physicians and pharmacists are being developed to improve the management of hypertension. The physicians often refer selected patients to the pharmacist for follow-up between office visits. The pharmacist may measure BP, adjust dosages, and alter treatment regimens established by the physician.<sup>7</sup>

A recent study demonstrated the value of the comanagement

in hypertensive patients by using a collaborative effort between physicians and pharmacists. The object of the study was to compare the effectiveness of an evidence-based approach with the treatment of hypertensive care through comanagement of patients by primary care physicians and clinical pharmacists versus the usual care (UC) given to patients. Patients with uncontrolled hypertension were randomized to either a UC regimen that was managed only by primary-care physicians or to a physician-pharmacist comanagement (PPCM) group. All physicians received group and individual education, and they all took part in developing an evidence-based hypertension treatment algorithm. Physicians were given the names of the patients with documented elevated BP ( $\geq 140/\geq 90$  mm Hg) for patients aged  $< 65$  years, ( $\geq 160/\geq 90$  mm Hg) for patients aged  $\geq 65$  years. Patients randomized to the PPCM arm of the study had the additional input of a clinical pharmacist who provided patient education, made treatment recommendations, and provided follow-up. Medical records provided data such as visit costs, antihypertensive medications used, and BP readings.<sup>8</sup> Figure 3 shows the results of the study.<sup>8</sup>

A total of 197 patients with uncontrolled hypertension participated in the study. Both arms of the UC (-11/-8 mm Hg) and PPCM (-22/-7 mm Hg) study showed significant reductions in BP ( $P < 0.01$  for both groups). Results demonstrated that a significantly larger number of patients achieved BP control in the PPCM group (60%) than in the UC group (43%) ( $P = 0.02$ ). The average visit costs per patient were significantly higher ( $P = 0.02$ ) in the UC group (\$195 per visit) than in the PPCM group (\$160 per visit).<sup>8</sup> The investigators concluded that an evidence-based, systematic approach to the management of hypertension using both a physician and clinical pharmacist resulted in improved BP control and a reduced cost average per visit per patient.<sup>8</sup>

### Academic Detailing to Improve Antihypertensive Prescribing Patterns

Studies have revealed that many physicians do not follow JNC recommendations on the treatment of hypertension. Likewise, they do not implement the recommendation made by the Medical Advisory Panel for the U.S. Department of Veterans Affairs (VA) that thiazide diuretics and  $\beta$ -blockers be used as first-line medications in the treatment of hypertension without comorbidities.<sup>9</sup>

In an attempt to improve physician awareness of important prescribing guidelines, a program was established to train pharmacists as academic detailers. This pharmacist-physician interaction training was conducted at 5 VA medical facilities. The program comprised lectures, educational materials, provider profiling, and personal meetings with 25 to 50 providers. Prescribing patterns for hypertension were determined over two 6-month periods (March 1, 1998, to August 30, 1998, for baseline; March 1, 1999, to August 30, 1999, for follow-up).<sup>9</sup> Following this intervention program, the



proportion of patients receiving CCBs decreased significantly from 43% to 38% ( $P<0.001$ ), while the proportion of patients receiving  $\beta$ -blocker therapy or thiazide diuretics increased significantly from 58% to 64% ( $P<0.001$ ). In hypertensive patients with DM, the proportion receiving an ACE inhibitor or ARB significantly increased from 72% to 76% ( $P<0.001$ ). In hypertensive patients with congestive heart failure, the use of these agents significantly increased from 74% to 78% ( $P<0.001$ ). An increase was also seen in the use of  $\beta$ -blockers in hypertensive patients with coronary artery disease ( $P<0.001$  for change from baseline). Further, after academic detailing, the prescribing patterns more closely followed national guidelines.<sup>9</sup> Increased physician awareness of the value of following guidelines developed by expert national panels may therefore help improve both the quality and the economy of antihypertensive treatment.<sup>9</sup>

### Expanded Roles for Community Pharmacists

Community pharmacists can become links between patients and physicians. Often, the pharmacist is the only member of the health care team with access to information about all of the patient's medications and so may be the only person aware of concurrent therapies prescribed by multiple physicians. The pharmacist can provide the physician with information about the number of prescription refills during a year—indicating a measure of adherence. Physicians may use this information when altering management strategies or making future treatment decisions. Medication costs to patients are always an important issue, and the pharmacist can assist in the development of cost-effective strategies that use JNC guidelines and recommendations from other recent consensus panels.<sup>7</sup>

Several studies have suggested that pharmacists can provide hypertensive patients with many services that were previously offered solely by physicians. Since hypertension is a disorder managed mainly by pharmacologic means, the involvement of trained, motivated, community pharmacists should benefit many hypertensive patients. One 5-month study demonstrated that the clinical services provided to hypertensive patients by a clinical pharmacist resulted in a significant improvement ( $P<0.001$ ) in patients' knowledge of hypertension and management, a significant increase in patient medication adherence ( $P<0.001$ ), and a significant increase in the number of patients whose BP stayed within normal range during the study ( $P<0.001$ ). The unique design of this study was that it included a baseline period, intervention period, and an evaluation after the intervention was discontinued.<sup>10</sup>

Data from this study conducted in 49 patients include the following:

- Scores obtained from a 21-question test designed to evaluate the patients' knowledge of hypertension and its management showed that the number of correct answers increased from 259 prestudy to 436 poststudy in the group that

**TABLE 2** Implementing the JNC 7 Guidelines<sup>2</sup>

#### Empathetic Reinforcement

- Express concern, hope, and interest in the patient's future
- Provide positive feedback
- Inquire into behaviors for achieving BP goal
- Conduct exit interview to clarify the regimen
- Schedule more frequent appointments and health care support for patients not reaching goal

#### Clinician Awareness and Monitoring

- Anticipate adherence problems for young men
- Consider nonadherence as the cause of failure to reach goal, resistant hypertension, sudden loss of control
- Encourage patients to bring in all medications, including over-the-counter products, to rule out iatrogenic causes of elevated BP
- Ask about pain medications
- Recognize and manage depression and other psychiatric illnesses
- Change unsuccessful regimens and search for regimens more likely to succeed

#### Care Delivery System

- Schedule the next appointment before the patient leaves
- Send appointment reminders and contact patients to confirm appointments
- Follow up when patients miss appointments
- Use an office-based system to monitor and follow up patient care

#### Patient Education and Treatment

- Assess patient's understanding and acceptance of the diagnosis
- Discuss patient's concerns and address misunderstandings
- Advise patient of BP reading and give a written copy
- Reach an agreement with patient on the BP goal
- Ask patient to rate his or her probability of following treatment (scale of 0 to 10)
- Inform patient about treatment and provide written information (standard brochures) about the influence of lifestyle—diet, exercise, supplements, alcohol
- Encourage patient's expression of concerns and questions; offer opportunities for the patient to state the appropriate treatment recommendations
- Emphasize that hypertension treatment must be continued, BP control does not equal cure, and BP must be measured to determine if it is elevated

#### Individualized Regimen

- Include patient in decision making
- Simplify the dosing (once daily, if possible)
- Incorporate treatment into patient's normal routine
- Reach agreement with the patient about short-term treatment and lifestyle goals
- Discuss diet and physical activity
- Encourage discussion about adverse drug effects and concerns
- Encourage self-monitoring with validated BP devices
- Minimize therapy costs and use community or national programs to assist with medication expenses
- Indicate that adherence to the treatment plan will be discussed at all appointments
- Encourage gradual, sustained weight loss

#### Social Support

- Involve family members and personal support groups in the treatment plan (with patient consent)
- Suggest group recreational activities

JNC 7 = Seventh Report issued by the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; BP = blood pressure.

received the services of a clinical pharmacist compared with 231 prestudy to 257 poststudy in the control group.<sup>10</sup>

- During the study period, the percentage of study patients who were compliant with drug therapy (defined as administration of 90% to 110% of prescribed doses) increased from 25% pretest to 79% in the study group compared with an increase from 16% to 17% in the control group. Both groups reverted to their pretest scores after the study. This latter finding indicates that simply implementing an intervention in hypertension is not sufficient for long-term results and that continued patient education, follow-up, and management are important to continue to achieve BP control.<sup>10</sup>
- The percentage of study patients who were normotensive (had an average DBP <90 mm Hg on 2 consecutive meetings) increased from 20% prestudy to 79% during the study period in the group that had the services of a clinical pharmacist but declined from 44% to 20% in the control group. Those percentages declined to 42% in the study group and to 14% in the control group after the study.<sup>10</sup>
- Average BP rates in the study group were 157/99 mm Hg prestudy, 146/90 mm Hg during the study, and 149/97 mm Hg poststudy in the study group. In the control group, average BP rates were 163/93 mm Hg, 166/101 mm Hg, and 168/103 mm Hg, respectively.<sup>10</sup>

Data from the results of another study indicated that when community pharmacists were trained and participated as members of the primary-care treatment team, significant ( $P<0.05$ ) improvements in patient satisfaction, BP control, and quality of life (QOL) were achieved. Known as the Taylorville Study, this was a controlled, single-blind, parallel-group study that evaluated pharmaceutical care provided to hypertensive patients and assessed the quality of care delivered by a model, interdisciplinary practice.<sup>11</sup>

The primary objective of the Taylorville Study was assessed by determining outcome variables at 6 months compared with baseline in 25 hypertensive patients randomly assigned to a study group. The control group consisted of 26 patients who were evaluated to determine if outcome variables remained constant from baseline to 6 months. Baseline SBP (151 mm Hg) was significantly reduced in the study group ( $P<0.001$ ) at 6 months (140 mm Hg). DBP was also significantly lower at 2, 4, and 5 months with baseline. Peer-rated review of prescribing data indicated a significant ( $P<0.01$ ) improvement in the appropriateness of the BP regimen, increasing from  $8.7 \pm 4.7$  to  $10.9 \pm 4.5$  in the study group, but showing no change in the control group. This study also revealed that QOL scores improved significantly ( $P<0.05$ ) in the study group after 6 months but did not change significantly in the control group. Overall, patient satisfaction scores were consistently higher in the study group at the end of the clinical trial. The investigators concluded that significant improvements in BP control, QOL, and overall patient satisfaction were accomplished when

community pharmacists were trained and included as part of the primary-care team.<sup>11</sup>

### **The Pharmacist's Role in Helping to Ensure Patient Adherence**

Patient nonadherence is a serious obstacle to the effective treatment of many acute and chronic disorders. Successful treatment and outcome of a chronic disease such as hypertension depend on many factors, including resources (e.g., funds, space, people), avoidance of serious adverse events, patient adherence with treatment plans, and the availability of effective therapies. The JNC 7 recommendations for supporting and sustaining patient treatment regimens are shown in Table 2.<sup>2</sup> The pharmacist is often in an ideal position to assist with patient education and monitoring to improve medication and lifestyle adherence. As noted above, studies suggest that using the clinical pharmacist to monitor BP improves patient adherence, drug documentation, and disease control.<sup>12</sup>

The results of a study among patients who received clinical pharmacy services at a VA medical center suggested that the intervention of a clinical pharmacist improved documentation of drug therapy and estimated patient compliance. Of 81 patients in the control group, 33% were judged to be compliant; of 113 patients in the study group, 85% were judged to be compliant. At 4 years, follow-up compliance in the study group was 88%, and BP was controlled in 90% of patients, while only 29% of patients in the control group had controlled hypertension.<sup>12,13</sup>

## ■ Results

### **The Pharmacist's Evolving Role in Health Care Delivery**

The expanded role of pharmacists in integrated health care delivery systems (e.g., VA medical centers, the Indian Health Service, and staff-model managed care organizations) includes participation in primary care teams. In this capacity, pharmacists assist with drug selection and monitoring, and they consult on the development of therapy guidelines and treatment pathways.<sup>7</sup> Additionally, more than 30 states now allow pharmacists to manage patients through collaborative agreements with physicians, and the majority of those collaborative arrangements are in integrated health systems.<sup>7</sup>

Another area in which the pharmacist's role is emerging is in physician office practices. Studies have shown that the long-term benefit of including a clinical pharmacist in a practice's program for patients with hypertension is cost effective. Primary savings are realized in fewer hospitalizations and reduced morbidity resulting from inadequately controlled BP.<sup>7</sup> In the community setting, the role of the pharmacist continues to evolve. Local pharmacists now assist physicians with monitoring patients who have hypertension—helping to improve patient adherence to therapy, reduce adverse events, and improve BP control. Many community-based pharmacists screen for new or uncontrolled hypertension and refer patients to physicians.<sup>7</sup> Given that almost every community has a

pharmacy,<sup>7</sup> that most people use only 1 pharmacy,<sup>7</sup> and that consumer confidence in pharmacists is very high<sup>7</sup>—the expanded role of the pharmacist as a member of primary-care teams can be a valuable asset for patients and physicians alike. As an integral part of an interdisciplinary team, pharmacists have an important contribution to make in achieving JNC goals for controlling hypertension.<sup>7</sup>

### Conclusions

Studies have demonstrated that the role of the pharmacist in the management of chronic diseases such as hypertension has increased in recent years. The pharmacist's role includes ensuring that recommendations provided by national guidelines such as the JNC 7 and the ADA in the treatment of hypertension are followed. It has been shown that when pharmacists are closely involved in the comanagement of patients with hypertension, greater reductions in BP are recorded, goal BPs are reached and maintained more frequently, patient QOL is improved, and more patients remain adherent to their medication regimens. In addition, when pharmacists become an integrated part of the primary care team, overall costs of therapy are better contained without sacrificing the quality of care. Pharmacist involvement in rural clinics, VA medical centers, and community hospitals has increased, and pharmacist participation has been positively acknowledged by medical staff and patients. Studies have also demonstrated that clinical pharmacy services are highly beneficial and enhance the long-term care given to hypertensive patients.

### DISCLOSURES

This article is based on the proceedings of a satellite symposium held March 31, 2004, at the Academy of Managed Care Pharmacy's 16th Annual Meeting and Showcase in San Francisco, California, which was funded by an unrestricted educational grant from Bristol-Myers Squibb Company and Sanofi-Synthelabo Inc. partnership. Author Barry L. Carter received an honorarium from Bristol-Myers Squibb Company and Sanofi-Synthelabo Inc. partnership for participation in the symposium upon which this article is based; he discloses that he participates in the Speaker's Bureau at Bristol-Myers Squibb Company and Merck & Company, Inc.

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**Posttest Answers:**

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## Continuing Education

### An Evidence-Based Approach: The Emerging Role of Renal Protection in Hypertension; A Focus on Clinical and Economic Factors That Impact Formulary Decision Making

Please indicate the correct answers on the Record of Completion.

- The mechanisms by which hyperglycemia leads to end-stage renal disease include
  - structural changes in the glomerulus.
  - hemodynamic changes in renal microcirculation.
  - interaction of soluble factors and cytokines.
  - All of the above
- Which of the following statements about microalbuminuria in patients with DM is *not* true?
  - Provides the first clinical manifestation of diabetic nephropathy
  - Occurs as soon as 5 years after the diagnosis of DM
  - Can progress to albuminuria and overt nephropathy within 10 years
  - Should be treated as soon as it progresses to albuminuria
- According to the U.S. Renal Data System Analysis, the most apparent recent increase in the ESRD population is for patients with a primary diagnosis of
  - hypertension.
  - diabetes.
  - glomerulonephritis.
  - Other disease
- Factors affecting the projected increase in costs associated with ESRD include the following:
  - With improved treatments, more patients with type 2 DM survive to experience ESRD.
  - Dialysis treatments are required for more patients because there is a shortage of kidneys for transplantation.
  - Expenditures for dialysis therapy, currently about \$50,000 per patient per year, are projected to increase due to rising costs for EPO and IV agents.
  - All of the above
- The RENAAL trial showed that, compared with standard hypertensive therapy, losartan therapy reduced the number of days with ESRD by 33.6% over 3.5 years, resulting in a savings of \$3,522 per patient in that time period.
  - True
  - False
- A recent analysis of the IDNT and IRMA II trial data using a Markov predictive model and a 25-year horizon showed that, when compared with standard hypertensive therapy, early use of irbesartan in 1,000 hypothetical patients with type 2 diabetes was
  - projected to save approximately \$11.9 million.
  - projected to add approximately 1,550 cumulative life years.
  - Both of the above
  - None of the above
- Diabetic nephropathy is usually diagnosed based on clinical grounds without a renal biopsy, and important clues to early diagnosis include
  - presence of normal-sized or enlarged kidneys.
  - evidence of proliferative diabetic retinopathy.
  - microalbuminuria or overt albuminuria.
  - All of the above
- Which is *not* a similarity of diabetic nephropathy in both type 1 and type 2 DM?
  - Time from onset of recognized diabetes to diabetic kidney disease
  - Underlying and generalized abnormality of the microcirculation
  - Degree of retinopathy directly correlated with the degree of renal abnormality
  - Risk factors, including glomerular hypertension and hyperfiltration, systemic hypertension, hyperglycemia, and hyperlipidemia
- Which statement about hypertension in patients with type 2 DM is *not* true?
  - Thirty percent of patients have high blood pressure at diagnosis.
  - The added problems associated with renal vascular disease contribute to hypertension in about 20% of patients.
  - The value of strict BP control in reducing albumin excretion in inhibiting the decline in renal function has not been clearly demonstrated.
  - ACE inhibitors and ARBS are the only agents shown to produce a drug-specific benefit in diabetic nephropathy independent of BP control.
- Blood pressure control in patients with diabetes should have the goal of maintaining BP at <130/85 mm Hg in patients without proteinuria and 125/75 mm Hg in patients with evidence of microalbuminuria or nephropathy.
  - True
  - False
- In the IDNT, patients with nephropathy due to type 2 diabetes received the ARB irbesartan, the CCB amlodipine, or placebo. Trial data show that
  - irbesartan therapy resulted in a lower risk of reaching the primary composite end point (doubling of baseline creatinine concentration, development of ESRD, or death from any cause) than did therapy with amlodipine or placebo.
  - proteinuria was reduced significantly more in patients who received irbesartan than in patients who received amlodipine or placebo.
  - therapy with irbesartan produced a reduction in the rate of progression of the nephropathy.
  - All of the above

12. Data from the RENAAL study showed that the ARB losartan, when combined with conventional antihypertensive therapy, decreased the level of urinary protein excretion and reduced the risk of ESRD. These data showed that
  - a. losartan therapy produced a statistically significant reduction in the risk of the primary composite end point (doubling of serum creatinine concentration, ESRD, or death).
  - b. losartan therapy combined with conventional antihypertensive agents (as required) provided strong renal protection and reduced BP in patients with type 2 diabetes and nephropathy.
  - c. Both a and b
  - d. None of the above
13. The COOPERATE trial, which assessed the effectiveness and safety of combined therapy with an ACE inhibitor (trandolapril) plus an ARB (losartan) compared with monotherapy with each agent in patients with nondiabetic renal disease, showed that
  - a. a distinct benefit of combination therapy was retardation of progression of renal disease for patients with high rates of urinary protein excretion and for those with small amounts of proteinuria.
  - b. there was no significant statistical difference in BP reduction among the 3 treatment groups.
  - c. combination therapy was well tolerated, even in patients with advanced renal insufficiency.
  - d. All of the above
14. Which statement about drug therapy for hypertension is *not* true?
  - a. The major classes of antihypertensive agents are thiazide diuretics, antiadrenergic agents, vasodilators, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.
  - b. Rational use of an agent depends on its site and mechanism of action and evidence supporting its use to decrease the rate of adverse outcomes related to hypertension.
  - c. The empirical approach to selecting an agent considers efficacy, safety, cost, impact on patient's quality of life, ease of administration, and patient adherence.
  - d. If antihypertensive agents are used in combination, they are chosen for their different sites of action.
15. The JNC 7 guidelines state that
  - a. in patients older than 50 years, systolic blood pressure >140 mm Hg is a clinically more significant factor for cardiovascular disease than the diastolic blood pressure.
  - b. patients who are normotensive at age 55 can expect to have a 90% lifetime risk of developing hypertension.
  - c. patients who are prehypertensive (i.e., 120 mm Hg to 139/80-89 mm Hg) require lifestyle changes to prevent progression to hypertension.
  - d. All of the above
16. The JNC 7 guidelines for treating hypertension state that treatment usually begins with lifestyle modifications (diet, weight loss, and exercise), but if BP goal is not reached, a thiazide diuretic should be introduced as initial therapy, either as monotherapy or in combination with another agent from one of the other classes of antihypertensives.
  - a. True
  - b. False
17. Data from a program implemented at 5 Veterans Affairs medical centers that utilized pharmacists as academic detailers for physicians showed that
  - a. the proportion of patients with hypertension receiving  $\beta$ -blocker therapy or thiazide diuretics increased significantly.
  - b. the proportion of patients with hypertension and DM receiving an ACE inhibitor or ARB increased significantly.
  - c. prescribing patterns followed national guidelines more closely.
  - d. All of the above
  - e. None of the above
18. A peer-rated review of the Taylorville Study data determined that a primary care team approach involving a pharmacist can significantly improve BP control in patients with hypertension and that in the study group
  - a. appropriateness of the BP regimen improved significantly.
  - b. patients' quality of life scores improved significantly.
  - c. Both a and b
  - d. None of the above
19. A study comparing an evidence-based approach to treatment of patients with uncontrolled hypertension by physicians only or by physician-pharmacist comanagement showed
  - a. no significant reductions in BP in either group.
  - b. significant reductions in BP for both groups, with a larger number of patients in the comanaged group achieving BP control.
  - c. significant reductions in BP for both groups, with a larger number of patients in the physician-treated group achieving BP control.
  - d. significant reductions in BP for both groups, with about the same number of patients in each group achieving BP control.
20. Evidence-based medicine that uses knowledge gained from large clinical trials
  - a. provides information to use in developing treatment guidelines.
  - b. promotes consistency in patient treatments that assume optimal clinical outcome.
  - c. facilitates making cost-effective formulary decisions.
  - d. All of the above

# PROGRAM EVALUATION

## An Evidence-Based Approach: The Emerging Role of Renal Protection in Hypertension; A Focus on Clinical and Economic Factors That Impact Formulary Decision Making

Participant's name: \_\_\_\_\_ Date: \_\_\_\_\_

Your assistance in the evaluation process is greatly appreciated. Please return this form with the posttest answers.

### Scale For Questions 1-5

- 1 = Not at all
- 2 = Not very well
- 3 = Somewhat well
- 4 = Well
- 5 = Very well

### Scale For Questions 6 and 7

- 1 = Poor
- 2 = Fair
- 3 = Good
- 4 = Very good
- 5 = Excellent

Using the scale above for questions 1-5, please rate how well you will be able to accomplish the following objectives based upon successful completion of the program.

Using the scale above for questions 6 and 7, please indicate the number that best expresses your opinion.

#### Objectives:

1. Outline strategies for the long-term management of hypertension and review American Diabetes Association (ADA) and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines; \_\_\_\_\_
  2. Discuss the evidence-based JNC 7 guideline recommendations and the application of these findings in patients with type 2 diabetes and kidney disease; \_\_\_\_\_
  3. Summarize the results of the 3 clinical trials that examined the effects of angiotensin II receptor blockers on the progression of renal disease in patients with type 2 diabetes; \_\_\_\_\_
  4. Differentiate the mechanism of action of angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors; and \_\_\_\_\_
  5. Evaluate the cost-effectiveness of angiotensin II receptor blocker therapy for controlling hypertension and diabetic nephropathy. \_\_\_\_\_
6. What is your overall rating of this program? \_\_\_\_\_
  7. How would you rate the pertinence of this program material to your practice? \_\_\_\_\_
  8. To what degree was there promotional bias? (check one)
    - a. Not at all \_\_\_\_\_
    - b. Somewhat \_\_\_\_\_
    - c. A great deal \_\_\_\_\_
  9. To what degree do you anticipate changes in patient care as a result of the material presented? (circle one)
 

1	2	3	4	5
No change			Significant change	
  10. Please indicate the length of time it took to complete this program. (circle selection(s))
 

Hours:	1	2	3
Minutes:	0	15	30 45
  11. Please rate the difficulty factor for completing this CE program. (circle selection)
 

Easy	Moderate	Difficult
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  12. Please rate your willingness to recommend this program to colleagues. (circle selection)
 

Very willing	Willing	Not willing
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  13. Please indicate which venue you prefer for obtaining continuing education. (circle selection)
 

Written monograph	Slides	Videos	Internet-based
Live sessions	Other: _____		



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## Supplement