Diabetes Intervention:
Achieving Tight Glycemic Control Through Combination Therapy

Proceedings of the National Association of Managed Care Physicians
Diabetes Advisory Board, Dallas, Nov. 11, 2000

HIGHLIGHTS

• NCQA/HEDIS 2000 Guidelines for Diabetes

• A Retrospective Study of Persistence With Single-Pill Combination Therapy vs. Concurrent Two-Pill Therapy in Patients With Hypertension

• Glucovance Clinical Overview

• Roundtable Discussion:
  Blueprint for Conversion of Patients on Metformin And Sulfonylurea to Glucovance

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Improving Diabetes Care

As greater numbers of Americans live longer and rates of obesity continue to climb, the prevalence of Type 2 diabetes is increasing with alarming speed. With 16 million diabetic patients in this country — a third of whom are undiagnosed — there is an undisputed need to improve diabetic care. For medical and managed care organizations, the financial effects of diabetes can be traced to complications that include heart disease, stroke, kidney disease, nerve disease, amputation, and blindness. Health plans that adopt aggressive new approaches to treatment will reap substantial clinical and financial benefits.

As efforts to raise standards of care escalate, HEDIS measures are increasingly used by consumers and purchasers of health insurance to make informed decisions. HEDIS standards outline minimum thresholds for quality care. In this article, Joe Smith, M.D., highlights the importance of the National Committee for Quality Assurance HEDIS diabetes measures, which estimate the percentage of diabetic patients receiving evidence-based care in four areas: blood sugar, lipids, retinopathy, and nephropathy.

Also in this publication, Christopher Dezii, R.N., M.B.A., discusses the compliance and persistence benefits of switching patients with hypertension from concurrent two-pill therapy to single-pill combination therapy. This potential for improved compliance and persistence can now be extended to diabetes patients with Glucovance (metformin HCl/glyburide), which eliminates complicated dosing regimens. Glucovance combination therapy is fast becoming a first-line therapy in diabetes treatment.

The pathology of diabetes demands early and aggressive treatment of this increasingly debilitating disease. Within these pages, Ann Seymour, Ph.D., examines data demonstrating the superior efficacy of Glucovance in reaching treatment goals in patients with Type 2 diabetes, when compared to monotherapeutic approaches. A clinical approach to converting patients from other treatment regimens to Glucovance is included in this section.

Late last year, medical directors, physicians, and representatives of pharmacy benefit managers convened in Dallas to identify appropriate patients for combination therapy. This publication concludes with an edited and condensed presentation of their roundtable discussion, for which I served as moderator, during which the group developed an effective managed care conversion blueprint from existing diabetes treatment plans within a patient population.

The importance of better diabetes management is clear: a progressive approach to care means enhanced patient quality of life.
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This MANAGED CARE Special Supplement, “Diabetes Intervention: Achieving Tight Glycemic Control Through Combination Therapy,” is supported by an educational grant from Bristol-Myers Squibb Company.

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<tbody>
<tr>
<td>Randall W. Killian, M.B.A., M.S. (moderator)</td>
<td>Executive Vice President</td>
<td>National Association of Managed Care Physicians</td>
<td>Glen Allen, Virginia</td>
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<td>Christopher Dezii, R.N., M.B.A.</td>
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<td>Bristol-Myers Squibb</td>
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<td>University of Houston, College of Pharmacy</td>
<td>Houston, Texas</td>
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<td>Medical Director</td>
<td>Pavonia Medical Associates</td>
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<tr>
<td>Kenneth Mayes, M.B.A., R.Ph.</td>
<td>Director, Prescription Benefit Management</td>
<td>Scott &amp; White Health Plan</td>
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<td>Lynne Milgram, M.D., M.B.A.</td>
<td>Medical Director, Sharp Community Medical Group</td>
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<td>Managed Health Care</td>
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<td>ProHealth Physicians</td>
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<td>Richard Seidner, M.D.</td>
<td>North Medical Family Physicians</td>
<td>Liverpool, New York</td>
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<td>Ann Seymour, Ph.D.</td>
<td>Director of Medical Development and Medical Education</td>
<td>Bristol-Myers Squibb</td>
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<td>Joseph Smith, M.D.</td>
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<td>Latham, New York</td>
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<td>Charles M. Stiernberg, M.D., M.B.A.</td>
<td>Medical Director</td>
<td>University Care Plus</td>
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<tr>
<td>Eric Toppy</td>
<td>Senior Product Manager</td>
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The addition of a new measure of comprehensive diabetes care to the set of widely used HEDIS measures has given top-flight managed care organizations (MCOs) yet another means to set themselves apart from the competition. Approximately half the MCOs in the United States participate in the accreditation process of the National Committee for Quality Assurance (NCQA). MCOs’ decisions to seek accreditation are partially business decisions. Plans participate because they know that large employers require NCQA accreditation. Moreover, NCQA accreditation satisfies the requirements now in place in 19 states for MCOs to undergo some form of external review; last year only 11 states required such review.

In 1999, NCQA introduced a new accreditation scale with five categories: Excellent, Commendable, Accredited, Provisional, and Denied. From a marketing perspective, the most important difference between the new scale and the old one, with its four designations (Full, which extends for three years; One-Year; Provisional; and Denied), is to allow the best-performing MCOs to distinguish themselves from their competitors. Whereas about 60 percent of MCOs previously were granted Full Accreditation, only about 10 percent now are deemed Excellent — and can market themselves as such. The Commendable rating is applied to the health plans that achieve full accreditation but fall short of the elite group; Accredited is the equivalent of the old One-Year Accreditation.

Part of an MCO’s accreditation score is determined by its performance on measures from the Health Plan Employer Data and Information Set (HEDIS), a set of performance measures that NCQA uses to look at the outcomes of care provided through MCOs. HEDIS scores also are used by consumers, government, and employers to compare the quality of MCOs. Thus, even MCOs that are not seeking NCQA accreditation participate in HEDIS; about 90 percent of HMOs nationwide submit HEDIS data to NCQA.

In 1999, Comprehensive Diabetes Care was introduced as an optional HEDIS measure, but it became mandatory in HEDIS 2000. This Effectiveness of Care measure applies to commercial, Medicare, and Medicaid product lines. For each product line, the MCO must report the percentage of continuously enrolled adult members (ages 18–75) with diabetes (Type 1 and Type 2) who met the following six criteria (the rationale for which is briefly explained):

**Hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) tested.** HbA\textsubscript{1c} is a derivative of the normal adult hemoglobin, hemoglobin A. Formed in small amounts during times when plasma glucose is elevated, it creates a record of past glucose levels, as elevated levels of HbA\textsubscript{1c} may persist in the bloodstream for up to 120 days. A patient’s plasma glucose is regarded as being well controlled if HbA\textsubscript{1c} is <7 percent, but if HbA\textsubscript{1c} is >8 percent, the patient is at increased risk for microvascular complications (retinopathy, nephropathy, neuropathy). In the largest and longest study of patients with newly diagnosed Type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS), it was found that every percentage point decrease in HbA\textsubscript{1c} reduced the risk of microvascular complications by 35 percent.

**HbA\textsubscript{1c} poorly controlled (>9.5 percent).** The reason poorly controlled HbA\textsubscript{1c} became the measure — as opposed to good, tight control — is that no consensus could be reached regarding the level of HbA\textsubscript{1c} that represents adequate control. But everybody could agree that HbA\textsubscript{1c} >9.5 percent indicates poor control. The usefulness of this measure was to be reevaluated after HEDIS 2000 data were submitted.

**Screening for LDL-C performed.** Dyslipidemia in pa-
Patients with Type 2 diabetes typically involve elevated levels of triglycerides and decreased levels of HDL-C; LDL-C concentrations tend to resemble those of patients without diabetes.

**LDL-C controlled to <130 mg/dL.** Although treating hyperglycemia reduces a patient’s risk of microvascular complications, it does little to reduce the risk of macrovascular disease. Given that two thirds of people with diabetes die from cardiovascular disease, therapy in Type 2 diabetes is aimed at reducing the risk of cardiovascular morbidity and mortality. The benefits of cholesterol-lowering therapy in patients with diabetes were demonstrated through subgroup analysis of long-term trials of gemfibrozil and several HMG-CoA inhibitors (statins).

**Dilated eye exam performed.** Diabetes is the leading cause of new cases of blindness among adults in the United States. The rationale for periodic eye exams rests on the efficacy of laser photocoagulation surgery to prevent vision loss, as shown by two studies sponsored by the NIH.

**Kidney disease monitored.** Testing for diabetic nephropathy is mandated because it has no clinical signs or symptoms in its early stages, but several therapies are available once it has been detected. Glomerular changes indicative of the early stages of diabetic nephropathy are identified by microalbuminuria, which is defined as an albumin excretion rate of 30–300 mg/day. An albumin excretion rate of >300 mg/day defines macroalbuminuria. Once macroalbuminuria has developed, renal function declines at a rate of 10 percent per year in diabetic patients, culminating in end-stage renal disease (ESRD) in 7 years. Treatment can delay progression to ESRD, but ESRD is almost inevitable once macroalbuminuria is present. Kidney monitoring therefore aims to identify microalbuminuria early enough to prevent or delay diabetic nephropathy.

This measure was developed through the Diabetes Quality Improvement Project, a collaborative effort that involved the American Diabetes Association, NCQA, the Health Care Financing Administration, the American Academy of Family Physicians, the Veterans Administration, the Foundation for Accountability, and the American College of Physicians.

Two other measures originally were envisioned as part of this set: foot exams and control of hypertension. However, DQIP participants decided that it is too hard to obtain adequate documentation about the performance of foot exams, and that hypertension is such a critical issue, it should become a stand-alone measure.

As noted, the measure of poor HbA1c control is being re-evaluated as part of NCQA’s continuous process of refining its HEDIS measures. However, this measure probably will be retained for a while, because on a regional basis there is wide variation of HbA1c levels, as defined by poor control (see table below). Nationally, according to data from HEDIS 2000, 44.8 percent of diabetic patients in health plans have poor HbA1c control, but the rate of poor control varies from 37.4 percent in the West North Central region to 51.6 percent in the South Central region.

### Elements of the HEDIS measure

The denominator for all six rates in HEDIS 2000 was a systematic sample drawn from the eligible population for each product line. The eligible population consists of continuously enrolled members ages 18 to 75 years as of

<table>
<thead>
<tr>
<th>U.S. Census Bureau region*</th>
<th>HbA1c testing</th>
<th>Poor HbA1c control</th>
<th>LDL-C screening</th>
<th>LDL-C control</th>
<th>Dilated eye exam</th>
<th>Monitoring diabetic nephropathy</th>
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<tr>
<td>New England</td>
<td>80.7</td>
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<td>South Atlantic</td>
<td>76.2</td>
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<td>38.3</td>
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<td>38.9</td>
<td><strong>67.7</strong></td>
<td>39.0</td>
<td>48.5</td>
<td>37.6</td>
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<tr>
<td>South Central</td>
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<td><strong>51.6</strong></td>
<td>68.6</td>
<td>34.4</td>
<td><strong>36.4</strong></td>
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<tr>
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<td>Mountain</td>
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<td>42.3</td>
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<td>42.3</td>
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<td><strong>National Average</strong></td>
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<td><strong>69.1</strong></td>
<td><strong>36.7</strong></td>
<td><strong>45.3</strong></td>
<td><strong>26.1</strong></td>
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Source: State of Managed Care Quality 2000, NCQA

Bold indicates region with the best percentage. Red indicates region with worst percentage.

*New England: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont; Middle Atlantic: New Jersey, New York, Pennsylvania; South Atlantic: Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia; West Virginia, District of Columbia; East North Central: Ohio, Indiana, Illinois, Michigan, Wisconsin; South Central: Alabama, Arkansas, Kentucky, Louisiana, Mississippi, Oklahoma, Tennessee, Texas; West North Central: Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota; Mountain: Arizona, Colorado, Idaho, Montana, New Mexico, Nevada, Utah, Wyoming; Pacific: Alaska, California, Hawaii, Oregon, Washington.*
Dec. 31, 1999, with Type 1 or Type 2 diabetes. Diabetic members are identified by pharmacy data and claims/encounter data. The former consists of ambulatory patients who received prescriptions during 1999 for insulin or oral hypoglycemics/antihyperglycemics; the latter group includes patients who had two different face-to-face encounters on two different dates in ambulatory or non-acute inpatient settings, or one face-to-face encounter in an acute inpatient or emergency room setting during 1999 with a diagnosis of diabetes.

The numerators for each of the six rates were calculated as follows:

**HbA1c testing.** This test was identified by a specified claim/encounter or automated laboratory record with a service date during 1999, or by a medical record that includes at least the date the HbA1c test was performed and the result.

**Poor HbA1c control.** If automated laboratory data or medical record review indicates that the last HbA1c level obtained during 1999 was >9.5 percent, the test was counted as indicating poor control. If no HbA1c value was available for 1999, the patient also was regarded as having poor control.

**Eye exam.** Administrative data (CPT and ICD-9-CM codes identifying eye exams) or medical records indicating that in 1999 the diabetic patient had a screening for diabetic retinal disease by an optometrist or ophthalmologist served as documentation. An eye exam performed in 1998 also could be counted if the member met at least two of three criteria: 1) no insulin was prescribed or dispensed in 1999, 2) the last HbA1c value from 1999 was <8 percent, and 3) an exam by an eye-care professional during 1998 showed no evidence of retinopathy, which must have been verified in the medical record.

**LDL-C screening.** An eligible LDL-C test was one performed in 1999 or 1998 and identified by specified CPT codes, or by a medical record indicating the date and result of the test.

**LDL-C level.** If the most recent LDL-C level obtained in 1999 or 1998 was <130 mg/dL, the LDL-C was regarded as controlled. The value must have been documented by automated laboratory data or by a medical record, both indicating the date and result of the test.

**Diabetic nephropathy.** This measure included patients who were screened for microalbuminuria in 1999 as well as patients with evidence (administrative data or medical records) of medical attention for nephropathy or a positive macroalbuminuria test.

There is every reason to believe that inclusion of the Comprehensive Diabetes Care measure among the other Effectiveness of Care measures in HEDIS will have the same beneficial effect as older HEDIS measures, which is to elevate the quality of care provided by MCOs nationwide.

**References**


A Retrospective Study of Persistence With Single-Pill Combination Therapy Vs. Concurrent Two-Pill Therapy In Patients With Hypertension

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Patients with hypertension often fail to control their blood pressure because they do not comply with pharmacologic therapy. In light of this, it has been hypothesized that a greater percentage of patients receiving a single pill combining an ACE inhibitor and a diuretic would persist with therapy than patients receiving both drugs as separate pills.

In the study discussed here, prescription data were obtained from a large commercial pharmacy benefit manager (PBM). The objective was to use pharmacy benefit data to retrospectively evaluate persistence with antihypertensive therapy consisting of combination therapy in a single pill vs. two-pill combinations.

In this study, the records of presumably newly diagnosed hypertensive patients for whom lisinopril combined with hydrochlorothiazide in a single pill (lisinopril/HCTZ) was prescribed were compared with those of patients for whom lisinopril and a diuretic were prescribed concurrently. Likewise, the records of patients for whom enalapril maleate combined with hydrochlorothiazide in a single pill (enalapril/HCTZ) was prescribed were compared with those of patients for whom enalapril maleate and a diuretic were prescribed concurrently. Patients were regarded as persisting if they renewed their prescription within 3 times the number of days supplied by the previous prescription. Patients were followed for 1 year from the date of the initial prescription.

At 12 months, the percentages of patients persisting with lisinopril/HCTZ (68.7 percent) and enalapril/HCTZ (70.0 percent) therapy were 18.8 percent and 21.7 percent greater, respectively, than the percentages of patients persisting with lisinopril plus concurrent diuretic therapy (57.8 percent) or enalapril maleate plus concurrent diuretic therapy (57.5 percent). Statistical significance (P<0.05) was demonstrated at 6 and 12 months for both comparisons.

It can be seen, then, that simplification of a drug regimen by using combination therapy in a single pill for hypertension resulted in significant increases in persistence with prescribed therapy.

Importance of pharmacotherapy

In the United States, only about 25 percent of the 50 million people with high blood pressure have their hypertension controlled to <140/90 mm Hg. For most patients, behavior modification approaches that emphasize weight loss, increased physical activity, and smoking cessation fail to produce lasting results. Pharmaceutical therapy therefore becomes mandatory, yet it is difficult to maintain. Part of the problem is that many patients with hypertension are asymptomatic and otherwise healthy, so they find it difficult to understand why they need to take an antihypertensive agent every day when they generally feel fine. On top of this concern, monotherapy fails to control blood pressure in about 50 percent of patients, and that includes most high-risk patients, so a combination of drugs is required.

Combination therapy offers an advantage in that low doses of two antihypertensive agents tend to be more effective and better tolerated than higher doses of either drug alone, as has been shown with combination therapy using low-dose felodipine and enalapril (Morgan 1992).

While it is more effective than monotherapy, combination therapy increases the complexity of the dosing
The index date was the date on which a patient’s first antihypertensive prescription was filled. Patients were followed for 1 year post-index. Continuous eligibility was established through the presence of any kind of claim beyond the 1-year horizon. We compared data for patients who filled an initial prescription for the ACE inhibitor lisinopril combined in a single pill with the diuretic hydrochlorothiazide (n = 1644) to data for patients who filled initial prescriptions for lisinopril and concurrent therapy with a diuretic (n = 624). We also compared data for patients who filled an initial prescription for the ACE inhibitor enalapril maleate combined in a single pill with hydrochlorothiazide (n = 969) to data for patients who filled initial prescriptions for two-pill therapy with enalapril maleate and a diuretic (n = 705).

Patients were identified as not persistent with therapy if they failed to renew a prescription within 3 times the number of days supplied by each prescription. That is, a patient who filled a 30-day prescription would be allowed 90 days (3 x 30) to refill the prescription before being classified as not persistent with therapy. Failure to refill prescriptions did not have to be in consecutive months; patients were identified as not persistent if any three scheduled refills were not obtained. Mail order prescriptions were excluded.

**Patient persistence**

Retrospective data were obtained from the database of a national commercial PBM with 4.8 million members for patients who received certain antihypertensive agents between the second quarter of 1995 and the fourth quarter of 1999. An attempt to restrict the analysis to patients new to therapy was made by identifying specific agents (e.g., lisinopril, enalapril/HCTZ) in their PBM records and then looking backward into the pharmacy records for 6 months; if no antihypertensive agents were found, the patients were presumed to be new to therapy.

The combination of ACE inhibitors and diuretics has been found not only to be especially effective but also well tolerated — achieving appropriate blood pressure control in about 80 percent of patients (Skolnick 2000). In the present study, we compare the persistence rates with two ACE inhibitors prescribed concurrently with diuretics versus two products combining an ACE inhibitor and a diuretic in a single pill.

**FIGURE 1  Persistence curves for lisinopril and lisinopril/HCTZ***

(Lisinopril/HCTZ n = 1644, lisinopril n = 624)

*Statistical significance (P<0.05) demonstrated at months 6 and 12 for both comparisons.
Comparing the data

In both comparisons (lisinopril/HCTZ versus lisinopril plus a diuretic, and enalapril/HCTZ versus enalapril maleate plus a diuretic), a greater percentage of patients receiving oral combination therapy in a single pill were deemed to have persisted with therapy after 12 months, in comparison to patients who received the ACE inhibitor and a diuretic as separate pills.

Figure 1 shows the persistence curves for patients for whom concurrent two-pill therapy with lisinopril and a diuretic or the single-pill lisinopril/HCTZ was prescribed. At 12 months, 18.8 percent more patients remained on the single-pill combination therapy lisinopril/HCTZ than on concurrent therapy with lisinopril and a diuretic. Specifically, 68.7 percent of the lisinopril/HCTZ patients persisted with therapy, versus 57.8 percent of the patients receiving concurrent therapy.

Figure 2 shows the persistence curves for patients for whom concurrent two-pill therapy with enalapril maleate and a diuretic or the single-pill combination therapy enalapril/HCTZ was prescribed. At 12 months, 21.7 percent more patients remained on the single-pill combination therapy with enalapril/HCTZ than on concurrent therapy with enalapril maleate and a diuretic. Specifically, 70.0 percent of the enalapril/HCTZ patients persisted with therapy, versus 57.5 percent of the patients receiving concurrent therapy.

Evaluating differences

Comparing Figures 1 and 2, the persistence curves for the single-pill combination medications are virtually identical, as are the curves for the concurrent therapies. In both figures, the greatest dropoff occurs during the second month of therapy, during which time the decline in persistence with combination therapy is similar to the decline in persistence with concurrent therapy. Thereafter, the curves gradually diverge until, at 12 months, persistence with the two single-pill combination products is about 20 percent greater than persistence with concurrent therapy.

In a study of patients who discontinued antihypertensive therapy within 1 year (and who did not switch to a different therapy), the median time to discontinuation was about 3 months, regardless of the class or agent (Benson 2000). A Canadian study found that barriers to persistence occur in the early stages of therapy (Caro 1999a). Of 27,364 patients newly diagnosed with hypertension, 78 percent were persistent with therapy at the end of 1 year, compared with 97 percent of the 52,227 patients with established hypertension. After 4.5 years, persistence with therapy among patients with established hypertension was 82 percent, but persistence among newly diagnosed patients was only 46 percent.

It is possible that the simplified dosing regimen afforded by combination therapy would help at least some

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**FIGURE 2 Persistence curves for enalapril maleate and enalapril/HCTZ**

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(Enalapril/HCTZ n = 969, enalapril maleate n = 705)

*Statistical significance (P<0.05) demonstrated at months 6 and 12 for both comparisons.
newly diagnosed patients to persist with their antihypertensive therapy long enough for it to be of some benefit, which requires years of treatment, not mere months.

**Defining limitations**

Our study did not take therapeutic switches into consideration. That is, patients who modified their therapy by switching to another ACE inhibitor or, more likely, a drug from another class of antihypertensives would not have been captured by our analysis. Even though such patients might have remained persistent with antihypertensive therapy in general, they would have been classified as failing to persist with the therapies that were examined in our study. We previously studied the rate at which patients modified their initial antihypertensive therapy, however, either by switching to a different therapy or by adding another drug from a different class. Figure 3 depicts rates of such modifications over the course of 12 months of follow-up. Among the patients who began with combination therapy (n = 1426) or polytherapy (n = 2510), 30 percent in each group modified their therapy. More than 95 percent of these modifications involved the addition of a new drug rather than a switch. This supports the likelihood that modification patterns were similar in our study, and that little switching occurred. It should be noted that because these data date back to 1995, angiotensin II receptor blockers (ARBs) may be underrepresented when compared to current prescribing patterns.

Another limitation of our study is that it is restricted to PBM data that are not linked to medical records and clinical measures. Presumably, some patients were prescribed lisinopril or enalapril maleate because of heart failure or acute myocardial infarction instead of hypertension, although many of these patients would be expected also to be hypertensive. For patients with hypertension, persistence with therapy is not an end in itself. The immediate goal of therapy is to reduce blood pressure, toward the ultimate goal of reducing the risk of morbidity and mortality. The next steps would be to demonstrate that improved persistence as a result of single-pill combination therapy, as opposed to concurrent therapy, leads to reductions in blood pressure and, of course, improved clinical outcomes, given that lowered blood pressure is not an end in itself, either.

In a review of interventions to improve patients’ compliance, Haynes et al found that with antihypertensive

![FIGURE 3  Modification rates by class](image)

**FIGURE 3  Modification rates by class**

Not modified | Modified | No refill after first prescription
---|---|---
CCB | 6% | 35% | 59%
ACE | 7% | 32% | 61%
BB | 8% | 38% | 54%
Diar | 14% | 36% | 50%
Other | 9% | 38% | 53%
Comb | 9% | 30% | 61%
Poly | 3% | 30% | 67%

Abbreviations: CCB = calcium channel blocker (n = 3223), ACE = ACE inhibitor (n = 3106), BB = beta blocker (n = 1336), Diur = diuretic (n = 1169), Comb = combination therapy (two agents given as one pill; n = 1426), Poly = polytherapy (two agents given as two pills; n = 2510), Other (n) = 627.

SOURCE FOR ALL FIGURES: PROTOCARE SCIENCES, HERNDON, VA.
therapy, single-daily dosage was among the interventions that improved compliance — but even the most effective interventions did not result in substantial improvements in compliance (Haynes 1996). The Canadian Coalition for Blood Pressure Prevention and Control nevertheless recommends once-daily dosage and simplified treatment regimens as one of four means to improve compliance. This recommendation clearly implies increased use of single-pill combination products as initial therapy.

Meanwhile, in the United States, the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recommends monotherapy with a diuretic or beta blocker as initial pharmaceutical treatment for uncomplicated hypertension — after lifestyle modification has failed to reach goal — on the grounds that randomized controlled trials have shown improved outcomes (reduced mortality and morbidity) with these agents. Given the low percentage of patients with high blood pressure whose hypertension is controlled despite the presence of many effective agents, and given that failure to control hypertension often stems from patients’ failure to persist with therapy, it may be time to rethink our approach toward the treatment of hypertension in the United States.

Persistence with antihypertensive therapy has been shown to vary according to the choice of initial agent (Caro 1997; Caro 1999b). Providing patients with a positive experience — rapid effectiveness and minimal adverse effects — with their initial therapy may serve to improve long-term compliance. Combination therapy employing a single pill — particularly if one of the components is a diuretic — would seem to be a step in that direction. Our study does not establish the superiority of single-pill combinations of ACE inhibitors and hydrochlorothiazide over other possible combinations of antihypertensive agents; it does show, however, that a greater percentage of patients for whom lisinopril/HCTZ or enalapril/HCTZ are prescribed persist with therapy in comparison with patients for whom the components of those drugs are prescribed as concurrent medications.

**Conclusion**

The simplification of a drug regimen by using single-pill combination therapy for hypertension results in significant increases in persistence with prescribed therapy.

**References**


Glyburide/Metformin HCl Clinical Overview

Ann Seymour, Ph.D.
Director of Medical Development and Medical Education, Bristol-Myers Squibb

Glycovance is an oral medication that combines glyburide and metformin HCl, which offer complementary mechanisms for achieving glycemic control in patients with Type 2 diabetes. This article discusses the rationale for lowering HbA1c to below 7 percent as a treatment goal, and it reviews clinical trials that established Glucovance as therapy for reaching this goal when used as initial treatment for patients failing diet and exercise or as second-line treatment for patients failing sulfonylurea monotherapy.

It was shown previously that substantial reductions in the risk of retinopathy and nephropathy can be achieved by improving glycemic control through intensive insulin therapy instead of conventional insulin therapy. In the Diabetes Control and Complications Trial (DCCT), in patients with Type 1 diabetes (n = 1441) who were followed for a mean of 6.5 years, intensive insulin therapy reduced the occurrence of retinopathy by 63 percent, albuminuria by 54 percent, and neuropathy by 60 percent (DCCT Research Group 1993). The mean HbA1c for patients receiving conventional therapy was 9.1 percent, versus 7.2 percent in the patient group receiving intensive therapy.

Likewise, a Japanese study of patients with Type 2 diabetes (n = 102) showed a 69 percent reduction in the risk of retinopathy and a 70 percent reduction in albuminuria in patients receiving intensive insulin therapy for 6 years, compared to those receiving conventional insulin therapy (Ohkubo 1995). The patients receiving intensive therapy achieved a mean HbA1c of 7.1 percent, compared to 9.4 percent in the conventional-treatment group. As shown in the patients with Type 1 diabetes in the DCCT, improving glycemic control led to a reduction in the risk of microvascular complications, specifically, retinopathy and nephropathy.

An analysis of the DCCT data (Figure 1) clearly demonstrates the progressive increase in the relative risk of diabetic complications as the percentage of HbA1c rises. The relationship between hyperglycemia and increased risk of complications shows a tremendous advantage in terms of patient care when better glycemic control is achieved. In addition, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a 4-year follow-up of DCCT (DCCT/EDIC Research Group 2000) demonstrated the long-term benefits of early aggressive treatment of diabetes. At the end of DCCT, the intensive-therapy group had a 76 percent reduction in the risk of progression of retinopathy, compared to the conventional-treatment group. During the 4 years of the EDIC follow-up, HbA1c levels for the two groups tended to converge, with the glycemic control improving in the original, conventionally treated patients and increasing slightly in those originally assigned to intensive therapy. The reduction in the risk of progression of retinopathy, 75 percent at the end of EDIC, was similar, however, to that observed at the end of the DCCT. The results show that early, aggressive treatment pays off in the long term; the earlier and the more aggressive the control of glycemia, the better off the patient will be over time.

These data are complemented by the U.K. Prospective Diabetes Study (UKPDS), which showed that every 1 percent reduction in HbA1c resulted in relative risk reductions of 21 percent for any diabetes-related endpoint, 21 percent for diabetes-related death, 14 percent for fatal and non-fatal MIs, and 37 percent for microvascular complications (Stratton 2000).

Better management of hyperglycemia not only improves the quality of patients’ lives, but also improves the fiscal health of managed care organizations. As shown in Figure 2, complications of diabetes contributed $282.7 million in excess health care costs ($3,494 per person) in a managed care population with 85,000 patients in its diabetes registry (Selby 1997). In a large HMO, 3-year
medical costs (1993–1995) for patients with complications of diabetes increased by 4, 10, 18, and 28 percent when HbA1c increased from 6 percent (the upper limit of normal) to 7 percent, 8 percent, 9 percent, and 10 percent, respectively (Gilmer 1997).

The Third National Health and Nutrition Examination Survey (NHANES III), based on survey data collected between 1988 and 1994, showed that only 44.6 percent of adults with Type 2 diabetes had an HbA1c level <7 percent, which the American Diabetes Association regards as the treatment goal for patients with diabetes (Harris 1999). Among diabetic patients treated with oral agents, only 37.7 percent had an HbA1c level <7 percent.

The challenge of treating Type 2 diabetes is that it is a progressive disease. In the UKPDS, patients newly diagnosed with Type 2 diabetes had an average HbA1c of 9 percent. After 3 months of diet and exercise, their average HbA1c fell to 7 percent, but over time (15 years) their HbA1c levels gradually increased, regardless of their assigned treatment (UKPDS 1998).

The progressive increase in HbA1c levels apparently does not stem from a change in insulin sensitivity, which is approximately 50 percent of normal at diagnosis but remains constant over time. Rather, there is a progressive decline in beta cell function (the ability of the pancreas to release insulin in response to a glucose load) that coincides with the rise in HbA1c. At the time of diagnosis, patients enrolled in UKPDS had about 50 percent of normal beta cell function. Thereafter, patients lost beta cell function at a rate of about 4 percent per year. Extrapolating the line that defines the decline in beta cell function during the UKPDS into the years before diagnosis, it becomes apparent that the decline in beta cell function began 8 to 10 years before diagnosis (Figure 3). During that time, the insulin resistance present at diagnosis did not worsen. Therefore, the progressive loss in glycemic control is associated with progres-
sive loss of beta cell function rather than worsening of insulin resistance.

Even though insulin resistance is often cited as the underlying cause of Type 2 diabetes, these data clearly demonstrate that there is also a basic malfunction in beta cells that is present at diagnosis and worsens with time. In and of itself, insulin resistance is insufficient to cause Type 2 diabetes. Insulin-resistant people, such as overweight individuals, are not hyperglycemic if insulin levels are high enough to compensate for that resistance. When beta cell function is abnormal, however, hyperglycemia results because the beta cell fails to secrete enough insulin to overcome the insulin resistance. Therefore, both the impaired ability of beta cells to respond to the glucose load and insulin resistance are targets for treatment for all people with Type 2 diabetes.

**Clinical trials with Glucovance**

Glucovance makes therapeutic sense because, through the complementary actions of glyburide and metformin, it targets the two major metabolic defects in Type 2 diabetes — insulin resistance and relative insulin deficiency. Glucovance was evaluated in a double-blind, placebo-controlled study involving patients who had failed to achieve glycemic control through diet and exercise \((n = 806)\). At entry into the trial, patients had been diagnosed with diabetes an average of 3 years previously. No patient had used an oral diabetes medication for at least 8 weeks prior to enrollment, and 75 percent of patients never had used an oral medication. To be enrolled, patients had to have a fasting plasma glucose (FPG) \(<240 \text{ mg/dL}\) and an HbA\(_{1c}\) level in the range of 7 to 11 percent.

After a 2-week placebo lead-in period, patients were randomized to one of five arms for 20 weeks: placebo \((n = 161)\), glyburide 2.5 mg \((n = 160)\), metformin 500 mg \((n = 159)\), glyburide 1.25 mg plus metformin 250 mg \((n = 158)\), and glyburide 2.5 mg plus metformin 500 mg \((n = 162)\). (The 1.25 mg/250 mg combination was developed out of a concern that the 2.5 mg/500 mg combination, commonly used in patients failing monotherapy, might cause hypoglycemia in patients who had failed to achieve glycemic control through diet and exercise.)

The dose of each medication could be increased by one tablet at weeks 4, 6, and 8, if mean daily glucose level was greater than 126 mg/dL over 3 to 5 days. The mean final doses for each group receiving active treatment were as follows: glyburide, 5.3 mg; metformin, 1317 mg; 1.25 mg/250 mg; 4.1 mg/824 mg for glyburide/metformin 2.5/500 mg. The primary endpoint of the study was the mean change in HbA\(_{1c}\) from baseline (8.2 percent) to week 20. The mean decrease from baseline HbA\(_{1c}\) was 1.48 percent in the Glucovance 1.25 mg/250 mg group, and 1.53 percent in the 2.5 mg/500 mg group (Garber 2000). In the glyburide and metformin monotherapy groups, HbA\(_{1c}\) decreased by 1.24 percent and 1.03 percent, respectively; the decline in the placebo group was 0.21 percent. More than 60 percent of patients who received either strength of Glucovance achieved an HbA\(_{1c}\) level <7 percent (Davidson 2000). Both forms of combination therapy also resulted in greater declines from baseline in FPG (Donovan 2000) and 2-hour post-prandial glucose (Rosenstock 2000) than either agent administered alone.

Hypoglycemic symptoms were reported for 11.4 percent of patients treated with glyburide/metformin 1.25 mg/250 mg, and 37.7 percent of patients treated with glyburide/metformin 2.5 mg/500 mg. Patients receiving glyburide/metformin 1.25 mg/250 mg reported fewer gastrointestinal adverse events (31.6 percent) than those receiving the 2.5 mg/500 mg combination (38.3 percent) (Garber 2000). These findings led to the recommendation of the 1.25 mg/250 mg formulation as the starting dose of Glucovance.
### TABLE 1 Patient conversion guides:
For converting patients from various combination therapies used in diabetes treatment

#### How to switch to Glucovance® from Glipizide/Glucophage® (metformin HCl tablets) combination therapy

<table>
<thead>
<tr>
<th>Current daily dose</th>
<th>Glyburide® Conversion ratio 1:1</th>
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<tbody>
<tr>
<td>5 mg</td>
<td>10 mg</td>
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<td>10 mg</td>
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<table>
<thead>
<tr>
<th>Conversion ratio</th>
<th>Glucophage® Switch to this dose of Glucovance</th>
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</thead>
<tbody>
<tr>
<td>0.5:1</td>
<td>2.5 mg/500 mg BID 2.5 mg/500 mg BID 5 mg/500 mg BID</td>
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<tr>
<td>1:1</td>
<td>2.5 mg/500 mg BID 2 tabs AM/1 tab PM 5 mg BID</td>
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<tr>
<td>2:1</td>
<td>2.5 mg/500 mg BID 2 tabs AM/1 tab PM 5 mg BID</td>
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#### How to switch to Glucovance® from Glyburide/Glucophage® (metformin HCl tablets) combination therapy

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<thead>
<tr>
<th>Current daily dose</th>
<th>Glipizide® Conversion ratio 0.5:1</th>
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<tr>
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<td>20 mg</td>
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<tr>
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<tr>
<td>0.5:1</td>
<td>2.5 mg/500 mg BID 2.5 mg/500 mg BID 5 mg/500 mg BID</td>
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<tr>
<td>2:1</td>
<td>2.5 mg/500 mg BID 2 tabs AM/1 tab PM 5 mg BID</td>
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#### How to switch to Glucovance® from Glucotrol XL® (glipizide) Extended Release Tablets/Glucophage® (metformin HCl tablets) combination therapy

<table>
<thead>
<tr>
<th>Current daily dose</th>
<th>Glucotrol XL® (glipizide) Extended release tablets Conversion ratio 1:1</th>
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<tbody>
<tr>
<td>5 mg</td>
<td>10 mg</td>
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<tr>
<td>10 mg</td>
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<table>
<thead>
<tr>
<th>Conversion ratio</th>
<th>Glucophage® Switch to this dose of Glucovance</th>
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<tbody>
<tr>
<td>0.5:1</td>
<td>2.5 mg/500 mg BID 2.5 mg/500 mg BID 5 mg/500 mg BID</td>
</tr>
<tr>
<td>1:1</td>
<td>2.5 mg/500 mg BID 2 tabs AM/1 tab PM 5 mg BID</td>
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<tr>
<td>2:1</td>
<td>2.5 mg/500 mg BID 2 tabs AM/1 tab PM 5 mg BID</td>
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</tbody>
</table>

#### How to switch to Glucovance® from Amaryl® (glimepiride tablets)/Glucophage® (metformin HCl tablets) combination therapy

<table>
<thead>
<tr>
<th>Current daily dose</th>
<th>Amaryl® (glimepiride tablets) Conversion ratio 2.5:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg</td>
<td>4 mg</td>
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<tr>
<td>4 mg</td>
<td>8 mg</td>
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<table>
<thead>
<tr>
<th>Conversion ratio</th>
<th>Glucophage® Switch to this dose of Glucovance</th>
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<tbody>
<tr>
<td>0.5:1</td>
<td>2.5 mg/500 mg BID 2.5 mg/500 mg BID 5 mg/500 mg BID</td>
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<tr>
<td>2:1</td>
<td>2.5 mg/500 mg BID 2 tabs AM/1 tab PM 5 mg BID</td>
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</table>

* Titrate as needed to maximum dose of 10 mg/2000 mg or 20 mg/2000 mg.
In order to avoid hypoglycemia, the starting dose of Glucovance should not exceed the daily dose of glyburide (or equivalent dose of another sulfonylurea) and metformin already being taken.
The daily dose should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose necessary to achieve adequate control of blood glucose.
Patients should be monitored closely for signs and symptoms of hypoglycemia following such a switch.
† Recommended daily and maximum doses based on package inserts.
‡ Glucotrol XL Extended Release Tablets is a registered trademark of Pfizer Inc.
§ Amaryl® is a registered trademark of Hoechst Marion Roussel.
study were directly enrolled in a 52-week open-label study, allowing them to receive Glucovance from the outset, as it was considered unethical for such patients to receive placebo. If their HbA1c was less than 9 percent, glyburide/metformin was initiated at 1.25 mg/250 mg BID, and if HbA1c was greater than 9 percent, the starting dose was 2.5 mg/500 mg BID. Final results for the 1-year study are not yet available, but interim results showed that the 144 patients who completed 26 weeks of treatment had a mean baseline HbA1c of 10.6 percent. Treatment with glyburide/metformin had reduced their average HbA1c to 7.1 percent after 13 weeks and 7.09 percent after 26 weeks. Likewise, their FPG dropped from a mean baseline of 283 mg/dL to 164 mg/dL after 2 weeks and 161 mg/dL after 26 weeks. These patients received mean doses of glyburide 7.9 mg and metformin 1571 mg.

In summary, patients who received glyburide/metformin as initial therapy achieved significantly greater reductions in glycemic parameters when compared to either metformin or glyburide monotherapy. Glyburide/metformin therapy achieved an HbA1c level of <7 percent in a greater proportion of patients than those receiving either agent as monotherapy, and it provided greater HbA1c-lowering at higher baseline HbA1c levels. Glucovance was found to be safe and effective at any HbA1c level. The interim results of the open-label study suggest that Glucovance may offer significant and rapid treatment benefits for patients with uncontrolled Type 2 diabetes while receiving diet and exercise therapy.

A second trial was conducted in patients with Type 2 diabetes inadequately controlled on sulfonylurea monotherapy, as indicated by HbA1c greater than 7.4 percent at screening. During a 2-week lead-in period, all patients were titrated to the maximum recommended glyburide dose of 20 mg/day delivered in split doses. If at the end of the 2 weeks, fasting plasma glucose was 126 mg/dL or higher, the patients (n = 639) were eligible for randomization. During the treatment phase, patients continued glyburide therapy (20 mg/day) or were switched to 500 mg/day of metformin, 2.5 mg/500 mg glyburide/metformin or 5 mg/500 mg glyburide/metformin. Metformin or glyburide/metformin was titrated to up to 4 tablets/day as needed for glycemic control.

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**TABLE 2  Recommended Glucovance starting doses**

**INITIAL THERAPY†‡**

| Initiate: For newly diagnosed patients with type 2 diabetes | HbA1c ≤ 9% | Glucovance 1.25 mg/250 mg QD with a meal |
| HbA1c > 9% or FPG > 200 mg/dL | Glucovance 1.25 mg/250 mg BID with meals |

**SECOND-LINE THERAPY**

| Replace: In patients not adequately controlled on either glyburide (or another sulfonylurea) or metformin alone | HbA1c ≥ 7% | Glucovance 2.5 mg/500 mg BID with meals |

| Switch: In patients previously treated with combination therapy with a sulfonylurea and metformin |  |

Glucovance 2.5 mg/500 mg with meals or 5 mg/500 mg with meals
Not to exceed total daily doses already being taken

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*Titrate as needed to maximum dose of 10 mg/2000 mg or 20 mg/2000 mg.
†Glucovance 5 mg/500 mg should not be used as initial therapy, due to an increased risk of hypoglycemia.
‡Dosage increases should be made in increments of 1.25 mg/250 mg per day every 2 weeks up to the minimum effective dose necessary to achieve adequate control of blood glucose.

In order to avoid hypoglycemia, the starting dose of Glucovance should not exceed the daily dose of glyburide (or equivalent dose of another sulfonylurea) and metformin already being taken. The daily dose should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose necessary to achieve adequate control of blood glucose. Patients should be monitored closely for signs and symptoms of hypoglycemia following such a switch.
The demographics of this patient population were similar to that of the first-line study except that the duration of diagnosed diabetes was longer and mean baseline HbA1c (9.5 percent) and FPG (approximately 215 mg/dL) were higher. At the end of the 16-week study, it was clear that continuing glyburide monotherapy or switching to metformin monotherapy provided no improvement in glycemic control. HbA1c was reduced from baseline by 1.5 percent in both groups receiving glyburide/metformin, however. With glyburide/metformin treatment, HbA1c was 1.7 percent lower than with glyburide and 1.9 percent lower than with metformin. Consequently, approximately 25 percent of patients taking glyburide/metformin had HbA1c <7 percent compared to only 3 percent of the patients remaining on monotherapy.

In conclusion, the first-line study was the first demonstration in a large, double-blind, randomized trial that simultaneously treating the metabolic defects of insulin resistance and insulin deficiency provided better glycemic control than monotherapy in patients failing diet and exercise. Furthermore, glyburide/metformin was superior to continued monotherapy in patients uncontrolled on sulfonylureas. Therefore, Glucovance provides benefits as initial pharmacological therapy for patients with Type 2 diabetes or as replacement therapy for patients who are uncontrolled on monotherapy. In addition, patients receiving polytherapy for Type 2 diabetes may be able to be switched to Glucovance, with attendant gains in compliance.

References
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Medical Director
University Care Plus
Houston, Texas

Randall Killian, M.B.A., M.S.: This group has been gathered together based on your unique combination of knowledge and experience in the area of diabetes treatment. This morning we looked at the new Comprehensive Diabetes Care measure in HEDIS 2000 and reviewed the treatment and compliance advantages of a new single-pill combination therapy — Glucovance — for Type 2 diabetes. Finally, we looked at how to convert many of your Type 2 diabetes patients from various combination therapies to Glucovance.

At this point, we’d like you to look at developing a blueprint, or a set of guidelines, to implement an effective patient-conversion strategy for Glucovance with your physician groups. Consider, if you would, how to take those many thousands of lives and systematically carry out this conversion in the management of your Type 2 diabetes patient population.

Dr. Seidner, by way of introduction, please tell us something about your practice. Also, share with us, if you would, how you go about identifying patients who are eligible for conversion to combination therapy.

Richard Seidner, M.D.: I have been a member of the North Medical Family Practice group for 11 years and in private practice for 35 years in Syracuse, New York. My objective is to help educate physicians and health care providers on the topic of diabetes. I have a large diabetes practice, and my colleagues and I get letters from managed care executives all the time emphasizing the impor-
tance of the switch to something that offers tight
glycemic control as well as convenient dosing.

The first question a practice has to address is
how best to go about switching all the patients
over, because there is some ambiguity as to the
role of the physician in implementing the con-
version process. I also would like to emphasize
that the way we are attacking this disease presents
challenges, one of which is to increase commu-
nication between physicians and their patients.

Many physicians have seen, however, that it is
possible to convert patients and achieve tight
glycemic control by using phone intervention
programs. To carry this out, the idea is to have the
staff identify the patients to be targeted for con-
version through chart pulls. We look at the charts
for HbA1c levels, as well as concurrent condi-
tions such as hypertension and renal disease. The
physicians then make calls, emphasizing to the
patient all the advantages of combination ther-
apy, including the added advantage of one phar-
macy copayment rather than two. Obviously, to
most effectively convey the importance of mak-
ing the switch, the physician should be the one
who calls the patient.

There are very few people for whom we mea-
sure antibodies. We look at peptides, but the
main issue is insulin resistance and, for this, we
use the HbA1c scores. Secondly, we look at the sul-
fonylureas. Insulin resistance remains the same,
whereas the sulfonylureas increase the amount of
circulating insulin but not the utilization of the
same. We also look at how long the diabetes has
been present and whether the patient will react
to pancreatic stimulation.

The ideal situation would be one where you
prescribe Glucovance and the patient ex-
periences minimal side effects that are
going to subside. Glucose is going to be
tightly controlled from this combination.

VICTOR MARCHIONE, M.D., F.C.C.P.: I work
at one of the largest private groups in New
Jersey. I am the medical director of a 65-
physician practice, and the proximity of
this group to New York City challenges us
to stay on the cutting edge continually
while surviving financial stress.

The idea is to identify the target groups
and benefit from the conversion of these
patients. By looking at diabetes mellitus
ICD-9 codes in general, you can use the
office charts to identify patients with that
coding on more than one or two visits.

We have found we can eliminate over-
loading the practitioner with unnecessary
office visits by using phone calls to follow
up with patients. By screening those calls,
we can get back to the patient who has
been targeted for the conversion.

For the physician, such calls amount to
what can be termed a “soft visit.” This has
been an innovative approach in working
with groups, and it provides a unique op-
portunity to streamline this process.

KILLIAN: What approaches are you finding
most effective for educating physicians as
well as patients about Glucovance?

MARCHIONE: The clinical piece has been
addressed through a series of educational
lectures. As for patient education, for the
most part, we have found that the take-
home material we either give or mail to the
patient is not particularly effective. Our

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NAMCP step-care process for switching appropriate* Type 2 diabetes patients to Glucovance®

<table>
<thead>
<tr>
<th>I. Medical group director/administrator</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Announce conversion program in medical group newsletter or bulletin</td>
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<tr>
<td>B. Send letter to PCPs and specialists</td>
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<table>
<thead>
<tr>
<th>II. Staff identifies current therapy</th>
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</thead>
<tbody>
<tr>
<td>A. Patient profiling (HbA1c ≥ 7 percent)</td>
</tr>
<tr>
<td>B. Pull charts</td>
</tr>
<tr>
<td>C. Flag charts</td>
</tr>
<tr>
<td>D. Identify patients’ providers</td>
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<table>
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<tr>
<th>III. Physician intervention</th>
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</thead>
<tbody>
<tr>
<td>A. Notify patient by phone or letter about conversion</td>
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<tr>
<td>1. Define advantages of single-pill combination</td>
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<tr>
<td>a. Tighter glycemic control</td>
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<td>b. One copayment vs. two</td>
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<tr>
<td>c. Improved compliance and convenience</td>
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<tr>
<td>B. Perform in-office patient test: HbA1c</td>
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<tr>
<td>C. Call pharmacy to change prescription</td>
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<tr>
<td>D. Schedule regular patient follow-up care</td>
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<thead>
<tr>
<th>IV. Pharmacy involvement</th>
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<tbody>
<tr>
<td>A. Medical group administrator or director sends a letter to pharmacy with list of patients targeted for conversion</td>
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<tr>
<td>B. Pharmacist communicates benefits of conversion to patients</td>
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* Appropriate patients are those who are on concurrent combination therapy of metformin and any sulfonylurea, or patients on monotherapy with HbA1c ≥ 7 percent.
experience has shown us that targeting those interested in diabetes management is much more effective than a general mailing.

**KILLIAN:** Thank you, Dr. Marchione. Dr. Hayes, how does your group approach the implementation of a conversion to combination therapy?

**J. DAVID HAYES, Pharm.D.:** I practice with the Kelsey-Seybold Clinic in Houston, a large IPA of about 290 physicians. My role is to provide clinical support to pharmacy administration, internal medicine, and family practice. I am a participating member of both the P&T committee and the diabetes advisory committee. Our organization captures about 30 percent of our prescription business within our pharmacies, because it’s not a closed system. Generally, in a closed system, you can approach it from the pharmacy.

**KILLIAN:** Dr. Roselli, what has been your experience in terms of carrying out such conversions within a patient population?

**ANTHONY ROSELLI, M.D.:** I am a general practitioner and a member of a 165-physician primary care group near Hartford, Conn. I am also the medical director of clinical research for this group.

Five years ago, I was involved with a similar conversion program that was being done with blood pressure patients. We identified the targeted group using the ICD-9 codes, and our office manager followed this up with calls to the patients. The personal nature of the call is what makes this a valuable part of the process. Of those patients called, 90 percent agreed to make the switch to the combination drug. So, it was a highly successful program.

Another way to do a Glucovance conversion is to first get buy-in from the P&T committee, along with administrative approval to partner with one of our large HMO plans. We would have to isolate our diabetes population that is specific to the HMO plan. This could be achieved through ICD-9 codes. Assuming we were able to collect that data through a good computer system, we could then meld our encounter data with the plan’s medical and prescription claims data to determine which patients may benefit from a conversion and to identify their primary care physician or specialist.

Now, the question arises as to whether we consider patients who are well controlled or those who are not — or both. We would need to define those who are not well controlled. The use of an HbA1c of 8 or greater may suffice, as this is the threshold for further treatment efforts advocated by the American Diabetes Association.

**HAYES:** Ultimately, the physician is the person you have to persuade that a conversion is in patients’ best interest. We can get over that hurdle by sending the physician a letter that outlines the program and listing his or her eligible patients, along with a return-approval letter. Assuming that we all have initial buy-in from the providers, we could also send the patient a letter and/or flag patient charts. These are all effective methods to use for implementing the conversion to this drug that will bring glucose under tighter control.

**KILLIAN:** When you send a letter to the doctors, who should that come from?

**HAYES:** It should come from the chairman of the P&T committee or some executive medical professional, such as a medical director or pharmacy director. The letter should state that we have identified that these patients fit the criteria for the diabetes program discussed in our bulletin or newsletter. The letter would also explain that it is just a matter of being aware that we’re now going to flag the chart for them — and this is where it has to depend on the physician. We could then send the patient a letter, depending on the level of buy-in from our complete system.

**KILLIAN:** Do you think that would work?

**HAYES:** I do, because you’re basically covering all your bases in that you’re receiving approval from the physician and then notifying the patient. Moreover, you’re going that extra step by flagging the chart. To follow it up, we would track those eligible individuals to determine the conversion rates and therapeutic benefits.

**KILLIAN:** What are the challenges that pharmacy faces in this area, Dr. Milgram?

**LYNNE MILGRAM, M.D., M.B.A.:** As the medical director of Sharp Community Medical Group, in San Diego, my role is to oversee the utilization and the quality in the pharmacy, and my main task is keeping the group solvent — a particular challenge in California. My interest in this discussion is rooted in my search for the most cost-effective ways to manage the population. Collecting accurate data to help analyze utilization patterns presents a challenge, as does the ten-
dency to underdiagnose this disease, which leads to unforeseen costs. I think Glucovance is a home-run drug.

KILLIAN: Thank you. That’s great. Glucovance is included in about 92 percent of formularies, so this combination product is available to many patients.

Dr. Hayes, do you have anything to add regarding the pharmacy’s role in the conversion process?

HAYES: There is another way we can implement a conversion strategy, which is just to look at our pharmacy, the 30 percent we capture, and identify those patients who are on combination therapy. Then we would send the physician the letter about the patients targeted for conversion. The next time those patients come in to get their scripts, we would inform them about the combination product, Glucovance, and ask if they would like to be converted. This would be of immediate value to patients because it saves them a copayment.

KILLIAN: Should that counseling be formalized?

HAYES: We counsel in our normal everyday business, but I also think the physicians need to know exactly what is going on so they can feel comfortable with this.

“Physician education, through direct mailings from pharmacy and therapeutics committees and medical directors, is an important part of getting the word out.”

KILLIAN: How about a handout to the patient to read about what is occurring?

HAYES: I think that any type of educational patient literature is great if the patients read it — and, of course, not so great if they don’t. Certainly, whenever you have literature, as a pharmacist, you can go through it step by step with the patient, or at least, point it out when the patient comes in for the prescription.

MILGRAM: An ongoing study in my medical group has demonstrated that even with interventions, our patients still do not achieve good glucose control. This leads me to believe that many physicians who are overwhelmed due to time constraints are not able to effectively treat patients in a way that meets goals. My group relies on a pharmacy benefits department to help the physicians. The pharmacy company can assist the management services organization with forms, manpower for the phones, and so on.

Also, to go beyond the efforts we make to educate physicians prior to conversion, I like the idea of providing the patient with information about the conversion if he or she goes to the pharmacy. We deal with over a hundred local pharmacies, so this would be an effective approach to patient education.

KILLIAN: We’ve talked about educating the docs, and you’ve raised many good points about the pharmacists playing an important role in patient education. How about continuing education for the pharmacist?

HAYES: That certainly would be important for them, because the pharmacists then would feel comfortable with facilitating the conversions. This is similar to direct-to-consumer marketing, and I think it’s a constructive way to approach this as long as you have physician approval.

MARCHIONE: I also wanted to bring out that rather than the retail chain pharmacies, in my town there are still mainly mom-and-pop drug stores that really don’t go through all these steps.

HAYES: Well, I think you have to target them and conduct similar programs.

KENNETH MAYES, M.B.A., R.Ph.: My group is an integrated health system in Central Texas, with over 500 physicians in a group practice clinic. As part of our patient base, we have a health plan with about 170,000 members. My primary responsibility within the managed care pharmacy department is the area of prescription benefit management. Major challenges being faced now are the development of an interdisciplinary approach to health care and finding ways the pharmacy can get involved in data management and the management of diabetes, especially in terms of therapy compliance.

The compliance issue actually fits into pharmacy well, because the pharmacy typically has more direct and regular contact with patients than do the medical groups. In most systems, the pharmacy has access to the most current and accurate prescription-claims data, and gets the data earlier than the health plan or medical group.

A Glucovance conversion program, as a means of improving compliance and persistence, could be administered through a pharmacy-based program. We would combine the effort with a medical-utilization review and conduct follow-up reviews for a quality-improvement project.

To implement such a program, after identification of our eligible diabetes patients, we would move to the next step, which is the physician let-
ter that lists their patients who qualify for the conversion. These letters would be returned to us for implementation. We would also communicate the physician’s decision to the patients and pharmacies.

Also, it is important to coordinate a consistent message to all involved parties. Communicating the benefits of the conversion to patients, such as fewer copayments, and notifying them that their physicians have approved the conversion, are essential aspects of this process. Continuous patient communication in terms of refill reminders and educational materials focusing on disease awareness must be provided as well, to maintain the compliance that is desired.

In addition to the usual newsletter and clinical communications to the physicians, I would suggest involving the pharmaceutical manufacturer’s representatives to convey the plan’s message to both the physicians and the pharmacy providers.

KILLIAN: Dr. Hayes, I’m curious about a barrier with respect to taking it from two prescriptions to one. Do you think that’s going to be a problem?

HAYES: No, I think it’s going to be a benefit. You can look, for example, at combination agents like Lotrel*, where conversions based on the databases have already been done successfully.

CHARLES STIERNBERG, M.D., M.B.A.: I am the medical director of a large, 450-member multispecialty group called Universal Care Plus, which is predominantly made up of the faculty of the University of Texas, in Houston. More than half of my time is spent seeing patients, and the rest of the time I am managing other physicians.

I basically find it helpful to try to get into the heads of the consumers to see what their needs are. We all have a good understanding of the needs of these patients and how much this product will benefit them, as well as the distributor, in terms of the cost.

Also, I’m interested in seeing what can be done to identify those millions that are not being treated. Perhaps there could be an Internet initiative, tracking whether a script is being filled.

Getting physicians on board with this product or any other new product is critical to success. The physician plays a central role in paradigm shifts that involve patient care, and conversion to Glucovance is no exception. Physicians who take care of these patients therefore must be well educated, and the best way to address this is through sponsored continuing medical education programs. Most doctors need CME not only to maintain their medical licenses but also to keep up with contemporary medicine.

A well-orchestrated CME diabetes management program that is well marketed would be an ideal mechanism to begin the process for converting Type 2 diabetes patients to Glucovance.

KILLIAN: Thank you very much, Dr. Stiernberg.

This morning’s discussion has shed valuable light on key aspects of the conversion process, and you’ve all raised some extremely useful suggestions for meeting the challenges health plans may initially face in switching their diabetes patients to single-pill combination therapy. It also seems clear that, as Dr. Milgram stated, this drug shows remarkable potential — both in terms of cost-reduction and treatment advantages.

At this point, let’s bring this meeting to a conclusion by summarizing the key points that have come out of our discussion.

We have established, first of all, that physician education, through direct mailings from pharmacy and therapeutics committees and medical directors, is an important part of getting the word out. In some instances, these letters could contain a list of patients who qualify for the conversions. These letters containing lists of targeted patients could also be sent to pharmacies to enhance patient-communication efforts.

In determining the patient group for which Glucovance is appropriate, we know that it is important to first identify the current therapy that the patient is on. This patient targeting can be best achieved by enlisting office staff to assist with chart pulls and patient profiling. The action steps that follow are initiated by the physician. The first step would be a call to inform the targeted patient about the transition to combination therapy. The patient then needs to be brought in for the HbA1c test, and the physician calls the pharmacist with the new prescription.

So, conversions to a better alternative are essentially made through direct physician intervention, which can be accomplished via phone in what has been termed a soft visit.

The benefits that Glucovance conversion brings to the patient are one copayment versus two, tight glycemic control at an appropriate price, and improved convenience and compliance. I am sure you all agree that what we have here is an extremely promising product that will greatly improve diabetes care.

Thank you all for your participation and your valuable contributions to this important program.

*Lotrel is a registered trademark of Novartis Pharmaceuticals.