Payer Implications of Clinical Practice Guideline Concordance in Type 2 Diabetes and Chronic Kidney Disease

By John A. Welz, MPH

Despite concerted efforts by the international healthcare community, diabetes continues to exact a staggering societal and economic toll worldwide, affecting about 220 million individuals. Global diabetes-related deaths are expected to double between 2005 and 2030. In the United States, 25.8 million individuals—or 8.3% of the population—have diagnosed or undiagnosed diabetes, and an additional 79 million American adults have prediabetes. Diabetes disproportionately affects older Americans; more than one quarter (26.9%) of persons aged 65 years and older have the disease.

Type 2 diabetes, the more prevalent form, accounts for about 90% to 95% of all cases and is usually first identified during middle age. Peak prevalence for initial diagnosis of type 2 diabetes is between the ages of 40 and 55 years and declines sharply after age 65. Of the estimated 1.9 million Americans newly diagnosed with diabetes in 2010, more than half were between the ages of 45 and 64 and nearly one quarter were younger than 45 years.

Hyperglycemia, the defining feature of diabetes, is associated with microvascular complications that are the cause of substantial morbidity, mortality, and cost. Microvascular complications of diabetes result from prolonged excess levels of glucose in the small blood vessels, supplying certain body tissues, and include retinopathy, a major cause of blindness; neuropathy, which is associated with amputation; and nephropathy, which can result in kidney failure. Diabetes is the primary cause of new cases of blindness among adults between the ages of 20 and 74 years, and...
it accounts for more than 60% of all nontraumatic lower leg amputations.²

Because diabetes is a leading cause of chronic kidney disease (CKD), which may culminate in end-stage renal disease (ESRD), the National Kidney Foundation (NKF) has established clinical practice guidelines regarding the use of oral antihyperglycemic drugs (OADs) in patients with diabetes and stage 3 to stage 5 CKD.⁴

This newsletter provides an overview of the microvascular complications associated with diabetes, focusing on diabetes-related CKD, and concludes with a comprehensive review of the clinical and economic ramifications of NKF-guideline nonconcordance in a representative sample of managed care members with diabetes and CKD.

**The Economic Burden of Diabetes**

A 2007 economic analysis published by the American Diabetes Association (ADA) estimated that diabetes was responsible for $174 billion in total annual medical costs.⁵ The analysis showed that one third of the total costs were attributable to diabetes-related complications (Figure 1). Treatment of the condition itself and general medical expenditures accounted for another 33%, and indirect costs, such as disability, work loss, and premature mortality, accounted for the remaining one third of the total.⁶ After adjusting for age and gender differences, average medical expenditures among persons with diagnosed diabetes were 2.3 times greater than expenditures would be in the absence of diabetes.⁷

Overall, inpatient hospital stays represent about half of all medical expenses attributable to the management of patients with diabetes.⁸ On a per-event basis, inpatient stays as a result of cardiovascular complications were more costly than any other chronic diabetes-related complication, averaging $3225 per hospitalization in 2007.⁹ Healthcare payers in the United States—including private managed care plans, hospitals, government entities such as Medicare and Medicaid, and self-insured employers—are responsible for managing the substantial medical costs associated with diabetes.

Patients with diabetes who have comorbidities use disproportionately more healthcare services than individuals with diabetes alone. In a recent study, a strong correlation was observed between the number of comorbidities and the use of primary care, ambulatory specialist care, and hospital admissions.⁶ In an analysis of the 2005 National Inpatient Sample, the ADA concluded that hospitalized patients have a longer average length of stay (ALOS) when diabetes is listed as a secondary diagnosis than when diabetes is not a complicating factor.⁷ In the analysis, complications were grouped as neurological, peripheral vascular, cardiovascular, renal, metabolic, general medical conditions, and other. The presence of diabetes contributed to a longer ALOS for all complications studied.⁸ For example, patients with diabetes admitted for a general medical condition that was identified as a comorbidity of diabetes experienced an ALOS of 13 days—almost 50% longer than the predicted ALOS if diabetes was not a complication.⁹

**Diabetes-Related Microvascular Complications**

The 3 microvascular complications related to diabetes are retinopathy, neuropathy, and nephropathy. In an analysis using data from the National Health and Nutrition Examination Survey (NHANES) 2005-2008, Zhang and colleagues found that 4.2 million (28.5%) persons with diabetes aged 40 years or older had diabetic retinopathy.¹⁰ Of these individuals, 655,000, or 4.4% of those with diabetes, had advanced diabetic retinopathy that could lead to severe vision loss.¹¹ Significantly more men than women (31.6% vs 25.7%) had retinopathy.¹² The risk for vision-threatening diabetic retinopathy was significantly higher in non-Hispanic blacks than in non-Hispanic whites, even after adjustment for all other factors.¹³ In this study, independent risk factors associated with the development of diabetic retinopathy included higher A1C levels, longer duration of diabetes, the use of insulin, and higher systolic blood pressure.¹²

Neuropathy is another microvascular complication of diabetes associated with significant morbidity and mortality.¹⁴ Some form of neuropathy occurs in approximately 60% to 70% of patients with diabetes.¹⁵ Similar to what is observed for nephropathy and retinopathy,
the risk for developing diabetic neuropathy is proportional to the magnitude and duration of hyperglycemia.\textsuperscript{8}

Diabetes-related neuropathies are heterogeneous, and symptoms can manifest as either focal or diffuse.\textsuperscript{9} Peripheral neuropathy of the extremities is relatively common; as a result, almost 30\% of individuals with diabetes aged older than 40 years report impaired sensation in their feet.\textsuperscript{5} Decreased pain sensation in the extremities can result in increased risk for skin breakdown and infection, in addition to injuries.\textsuperscript{9}

Patients with diabetic neuropathy accrue greater treatment costs than patients without neuropathy. In a database analysis comparing medical resources used by patients with and without diabetic neuropathy, costs for patients with diabetic neuropathy were more than 5 times higher than for patients with diabetes who did not have neuropathy, and inpatient costs were 7 times higher for these patients.\textsuperscript{10} Data also suggest that diabetic neuropathy may be underdiagnosed. The Glycemic Optimization with Algorithms and Labs At Point of Care (GOAL A1C) study showed that physicians prospectively identified only 31\% and 66\% of patients with mild-to-moderate and severe neuropathy, respectively, indicating that physicians underestimate neuropathy in many patients with type 2 diabetes and may be missing potential opportunities for early intervention.\textsuperscript{11}

**Diabetes and Chronic Kidney Disease**

As a consequence of the global epidemics of diabetes and obesity, type 2 diabetes is now one of the leading causes of CKD worldwide. It is estimated that diabetes accounts for 45\% of kidney failure cases, up from 18\% in 1980.\textsuperscript{4} The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative\textsuperscript{29} (NKF-KDOQI) estimates that CKD affects 11\% of the US population, with afflicted individuals at increased risk for cardiovascular disease and kidney failure.\textsuperscript{8}

**Figure 2. Prevalence of CKD among Patients with Diabetes**

<table>
<thead>
<tr>
<th>Stage</th>
<th>CKD prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>19.8%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>22.2%</td>
</tr>
<tr>
<td>Stage 3</td>
<td>17.8%</td>
</tr>
<tr>
<td>Stage 4-5</td>
<td>36.0%</td>
</tr>
<tr>
<td>No CKD</td>
<td>4.7%</td>
</tr>
</tbody>
</table>


**Figure 3. Incidence of Complications for Patients with Comorbid Diabetes and CKD**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence per 100 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>× 2.8*</td>
</tr>
<tr>
<td>AMI</td>
<td>× 2.2*</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>× 1.7*</td>
</tr>
<tr>
<td>PVD</td>
<td>× 2.1*</td>
</tr>
<tr>
<td>ASVD\textsuperscript{b}</td>
<td>× 1.9*</td>
</tr>
<tr>
<td>Death</td>
<td>× 2.5*</td>
</tr>
</tbody>
</table>

\textsuperscript{a} P < 0.0001.

\textsuperscript{b} Defined as the first occurrence of AMI, CVA/TIA, or PVD.

AMI indicates acute myocardial infarction; ASVD, atherosclerotic vascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; PVD, peripheral vascular disease; TIA, transient ischemic attack. Source: Reference 14.

Diabetes is far more common in persons with CKD than in those without the condition, and there is a general trend toward higher prevalence with increasing CKD stage (Figure 2).\textsuperscript{12} More than one third (36\%) of stage 4 and stage 5 CKD patients also have diabetes.\textsuperscript{12} Furthermore, it is estimated that almost 42\% of persons with undiagnosed diabetes and 18\% of persons with prediabetes also have some degree of CKD.\textsuperscript{13}

Based on data from the Medicare pop-
ulation between 1998 and 1999, Foley and colleagues demonstrated that the rates of major complications were higher for patients with comorbid CKD and diabetes than for patients without these conditions or with diabetes only (Figure 3, page 3). The researchers concluded that high death rates of patients with CKD may reflect accelerated rates of atherosclerotic vascular disease and congestive heart failure in senior populations.14

Diabetes is the leading cause of ESRD in the United States.7 According to 2008 statistics from the US Renal Data System, 174,660 (32.5%) patients with type 2 diabetes had ESRD.12 In 2008, diabetes (type 1 and 2) was responsible for 38.3% of all cases of ESRD, followed by hypertension, which was responsible for 24.8% of ESRD cases.12

**Chronic Kidney Disease: An Underrecognized Condition**

Despite the presence of significant comorbidities, CKD screening and documentation rates remain suboptimal. In 2008, only 34.2% of patients with diabetes and CKD received the recommended screening tests: at least 2 A1C tests, at least 1 lipid test, and at least 1 retinal eye examination.12

Guessous and colleagues investigated the prevalence and impact of major CKD risk factors—type 2 diabetes and hypertension—on the documentation of CKD by primary and subspecialty providers in a managed care population. A total of 10,266 patients with an estimated glomerular filtration rate (eGFR) of 10 to 59 mL/min/1.73 m² were included in the analysis.15 Although the prevalence of CKD documentation increased with the presence of hypertension and/or type 2 diabetes, in total, only 14.4% of patients had an event-based CKD diagnosis at baseline.15

Multivariate analysis showed significant predictors of CKD documentation to be older age, lower eGFR, peripheral arterial disease, congestive heart failure, and statin use.15 In all categories, CKD documentation was lower among women than among men. Overall, the prevalence of documentation in men and women with CKD and hypertension and CKD and diabetes was 30% and 19%, respectively.15

Patients also lack CKD awareness, with very few persons realizing that they have the condition. Using NHANES data, one study showed that only 3.7%, 3.5%, and 7.8% of patients with stage 1, 2, or 3 CKD, respectively, were aware of their disease.16 Even among patients with stage 4 CKD, only 41.8% were aware of their condition.16 Overall, more than 90% of individuals with CKD did not know that they had renal impairment.16

### The Impact of CKD and Diabetes on Payers

The presence of CKD in patients with type 2 diabetes increases costs for managed care.17 Laliberté and colleagues conducted a study to quantify the incremental direct all-cause healthcare costs among patients with CKD who have diabetes and/or hypertension. Medical claims and laboratory data from a managed care database were analyzed for approximately 30 million members enrolled in 35 health plans between January 1, 2000, and February 28, 2006. A total of 11,531 patients with diabetes, 74,759 patients with hypertension, and 4779 patients with diabetes and hypertension were included in the study.17

Among patients who developed CKD, all-cause mean annualized costs for patients with diabetes ($8829, P = 0.026), hypertension ($4175, P = 0.004), and diabetes and hypertension ($9397, P < 0.001) all increased significantly after the onset of CKD (Figure 4).17 All-cause medical costs were highest during the first 3 months after a diagnosis of CKD.17

Given the preceding healthcare cost disparity, it is not surprising that patients with both CKD and diabetes are at increased risk for hospitalization compared with patients with diabetes alone. In 2008, the adjusted hospitalization rate for patients with CKD who have diabetes was 726 per 1000 patient-years at risk—85% greater than the rate of 393 per 1000 among patients without diabetes.12

When renal impairment progresses to ESRD, total medical costs increase sharply. In a study evaluating direct medical costs before and after the onset of ESRD in a managed care population of patients with and without diabetes, total observed annual costs more than doubled from the pre-ESRD period to the post-ESRD period for both groups of patients.18

In patients with diabetes, costs increased from $36,554 to $86,081, and in patients without diabetes, costs increased from $22,881 to $57,249.18 Annual
renal-related costs increased 5-fold in patients with diabetes, from $14,738 to $69,439.\textsuperscript{15} The impact to the payer is significant. Commercial health plans are responsible for the care of ESRD patients for almost 3 years; therefore, they incur the bulk of ESRD-related costs.\textsuperscript{18}

The landmark UK Prospective Diabetes Study (UKPDS) demonstrated that the risk of microvascular complications in type 2 diabetes is strongly associated with hyperglycemia (based on mean A1C levels).\textsuperscript{19} According to the NKF, intensive glycemic control can delay the onset and progression of nephropathy.\textsuperscript{4}

Koro and colleagues used information from NHANES IV to evaluate glycemic control and antihyperglycemic drug use in type 2 diabetes patients at different stages of CKD.\textsuperscript{20} Study results indicated that the mean A1C level was lower as CKD stage progressed from stage 1 (mean A1C = 8.35%) to stages 4 to 5 (mean A1C = 6.63%), indicating that the degree of renal impairment was inversely correlated with glycemic control.\textsuperscript{20} These findings underscore the need for improved screening and treatment of patients with type 2 diabetes for CKD in accordance with established guidelines to prevent the cascade of events leading to nephropathy by implementing adequate glycemic and blood pressure controls, especially in the early stages of CKD.\textsuperscript{20}

**NKF Guideline Concordance in a Managed Care Population**

A study was conducted to evaluate the clinical and economic consequences of concordance with NKF treatment guidelines for OAD use in patients with type 2 diabetes and stage 3, 4, or 5 CKD. A population with diabetes from a large managed care organization’s electronic medical record database of more than 3 million patients was analyzed during the period between January 2005 and October 2010.\textsuperscript{21}

To be included in the analysis data set, patients were required to be taking at least 1 OAD, have at least 1 clinical encounter with a diagnosis of diabetes, and have at least 1 clinical encounter or laboratory test indicating stage 3, 4, or 5 CKD. The first occurrence of CKD was denoted as the index date for the analysis.\textsuperscript{21} CKD stage was determined according to NKF-recommended methodology and included both laboratory-based eGFR and estimated methods (using the Modification of Diet in Renal Disease equation) for determining renal clearance.\textsuperscript{22} Patients were included in the analysis based on their first diagnosis of CKD stage 3, 4, or 5. The multivariate regression model was adjusted for age, gender, race, Charlson comorbidity index, use of insulin, and CKD stage.\textsuperscript{21} The baseline demographics for the 2 groups are shown in the Table.

NKF guideline concordance was defined based on the NKF guideline recommendation for dosing adjustment of OADs in patients with CKD.\textsuperscript{4} Of 46,204 patients identified with diabetes, 28,671 met the inclusion criteria for the analysis.\textsuperscript{23} Of the patients with diabetes, 16,728 (58.3%) had CKD, of which 9072 (54.2%) had stage 3, 4, or 5 disease.\textsuperscript{23} After patient exclusions, a total of 6058 patients with diabetes and stage 3, 4, or 5 CKD were analyzed for NKF-guideline–concordant treatment with OADs.\textsuperscript{23} NKF-guideline–concordant treatment was assessed during a 3-month period immediately after the first observed indication of CKD.\textsuperscript{21}

The study cohorts were determined by categorizing all the patients into 4 discrete groups, in accordance with the following scenarios\textsuperscript{23}:
1. OAD requiring no dose adjustment
2. OAD requiring dose adjustment and adjusted properly
3. OAD requiring dose adjustment and not adjusted
4. OAD should be avoided completely.

### Table. Baseline Characteristics: NKF-Guideline–Concordant Treatment Study

<table>
<thead>
<tr>
<th>Patients, N</th>
<th>Concordant with NKF guidelines</th>
<th>Not concordant with NKF guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), yr</td>
<td>69.2 (11.3)</td>
<td>70.0 (11.0)</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>37.6</td>
<td>48.3</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>96.9</td>
<td>98.0</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>3.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Stage of CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>91.8</td>
<td>88.0</td>
</tr>
<tr>
<td>4</td>
<td>4.9</td>
<td>8.9</td>
</tr>
<tr>
<td>5</td>
<td>3.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Charlson comorbidity index, mean (SD)</td>
<td>4.4 (2.1)</td>
<td>4.7 (2.1)</td>
</tr>
<tr>
<td>Glycemic control (A1C &lt;7%), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>41.1</td>
<td>33.8</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>38.5</td>
<td>45.2</td>
</tr>
<tr>
<td>Missing</td>
<td>20.4</td>
<td>21.0</td>
</tr>
</tbody>
</table>

CKD indicates chronic kidney disease; NKF, National Kidney Foundation; SD, standard deviation.

For example, if a patient had records for 3 different OADs, and the first classified the patient into group 1 (receiving an OAD with no dose adjustment required), the second into group 2 (receiving an OAD requiring dose adjustment, dose adjusted), and the third into group 3 (receiving an OAD requiring dose adjustment, dose unadjusted), then that patient would have been classified into the least concordant scenario (ie, receiving an OAD requiring dose adjustment with the dose unadjusted [group 3]). If one OAD record classified patients into the non-guideline-concordant treatment group and the other OAD record had missing dose information, then that patient would have been classified into the non-guideline-concordant treatment group.23

Using the methodology described above to categorize patients, the analysis showed that 55% (N = 3361) of patients received NKF-guideline–concordant treatment, indicating that they were either receiving an OAD that did not require a dose adjustment or they were receiving an OAD that required a dose adjustment and the dose was properly adjusted (Figure 5).21

In contrast, 45% (N = 2697) of patients received treatment that was not concordant with NKF guidelines, signifying that they were either receiving an OAD that did not require a dose adjustment or they were receiving an OAD that required a dose adjustment and the dose was not adjusted (N = 525; 19%), or that they were receiving an OAD that should have been completely avoided (N = 2172; 81%).21

In terms of clinical events, patients who received NKF-guideline–concordant treatment showed significantly better glycemic control (defined as A1C <7.0%) and lower hospitalization rates than patients receiving treatment that was not concordant with NKF guidelines. As shown in Figure 6, at 12 months from the index date, a total of 46.1% of patients who received NKF-guideline–concordant treatment achieved glycemic control versus 36.1% of patients who received treatment that was not concordant with NKF guidelines (P <0.05).21 All-cause hospitalization rates were significantly lower for NKF-guideline–concordant patients.21

In addition, at 12 months, 54.3% of patients who had their dose adjusted patients with multiple OAD drug records were prioritized according to the following scheme23:

Scenario 4 > Scenario 3 > Scenario 2 > Scenario 1

Figure 5. NKF Guideline Concordance in the Study Population


Figure 6. Differences in Glycemic Control (A1C <7.0%) and Hospitalization Rates, by NKF Guideline Concordance and Dose Adjustment

*Indicates significant difference between cohorts at P <0.05.

NOTE: Only about 85% of patients had glycemic control data.

NKF indicates National Kidney Foundation.

properly achieved glycemic control, compared with only 36.8% of patients who did not have the dose adjusted correctly.\textsuperscript{21}

NKF guideline concordance with oral antihyperglycemic medications also had important economic consequences. Mean annual healthcare costs and mean annual diabetes-related costs were both significantly higher in the cohort that was not concordant with NKF guidelines compared with the NKF-guideline–concordant cohort (Figure 7). Mean annual healthcare costs were 15% higher ($11,357 vs $9865, respectively; \( P < 0.0001 \)) and mean diabetes-related costs were 22% higher ($8142 vs $6694, respectively; \( P < 0.0001 \)) for the group that was not concordant with NKF guidelines versus the NKF-guideline–concordant group.\textsuperscript{21} The difference was primarily a result of the higher mean cost of inpatient encounters.\textsuperscript{21}

Based on the regression analysis, treatment that was not concordant with NKF guidelines was associated with annual encounter costs that were 1.12 times greater than those associated with NKF-guideline–concordant treatment, translating to an increase of $839 per patient per year for treatment that was not concordant with NKF guidelines.\textsuperscript{21}

In this study, NKF guideline concordance was also associated with a lower rate of hypoglycemic events (Figure 8). Significantly fewer patients receiving NKF-guideline–concordant treatment experienced hypoglycemic events compared with patients who received treatment that was not concordant with NKF guidelines (10.2% vs 14.0%, respectively; \( P < 0.0001 \)).\textsuperscript{21}

Encounter costs related to hypoglycemic events were also higher in patients who did not receive NKF-guideline–concordant treatment ($525 per hypoglycemic event) versus patients receiving NKF-guideline–concordant treatment ($239 per event).\textsuperscript{21}

**Conclusion**

Diabetes is responsible for substantial societal and economic hardship worldwide and in the United States.\textsuperscript{1,2,5} Renal impairment is a common microvascular complication, and as a result, diabetes is one of the leading causes of CKD.\textsuperscript{4} Patients with diabetes and CKD, some of whom progress to ESRD, have a major impact on payers of healthcare in the United States.\textsuperscript{17,18} Clinical practice guidelines have been established to help providers to identify and stage CKD, as well as to recommend appropriate pharmacotherapeutic options for their patients.\textsuperscript{4} However, awareness of and adherence to guidelines are suboptimal, particularly among primary care practitioners.\textsuperscript{12,13}

In a study conducted to evaluate the impact of NKF guideline concordance on clinical measures and healthcare resource utilization in a managed care population, patients whose treatment was NKF guideline concordant demonstrated better clinical outcomes, including higher rates and likelihood of glycemic control, lower risk for hospitalization, and lower risk for hypoglycemic events compared with patients whose treatment was not
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NKF guideline concordant.21,23 Furthermore, patients whose treatment was NKF guideline concordant had lower total encounter costs, diabetes-related costs, and hypoglycemia-related costs compared with patients who were not NKF guideline concordant.21 These findings underscore the need to better educate providers regarding optimal identification and treatment strategies for patients with diabetes and CKD. ■

References

About the Author
John A. Welz, MPH, is a medical and managed care consultant. With more than 12 years of agency-based consulting and health plan experience, Mr Welz has expertise in strategic and tactical planning, formulary dossier development, and pharmacoconomic modeling.

In his previous role as a member of the Health Informatics team at HIP Health Plan of New York (now EmblemHealth), Mr Welz designed and implemented quality improvement initiatives to support health plan accreditation efforts, directed drug utilization experience analyses, and conducted health outcomes studies.

Mr Welz has presented original research on smoking cessation, diabetes, and hypertension at national health-care meetings, and is a member of the American Public Health Association.

Disclosure Statement
John A. Welz, MPH, received fair market value compensation for taking part in this activity.