ORIGINAL RESEARCH ARTICLE

Dis Manage Health Outcomes 2004; 12 (3): 181-188
1173-8790/04/0003-0181/$31.00/0

The Costs of Non-Adherence to Oral Antihyperglycemic Medication in Individuals with Diabetes Mellitus and Concomitant Diabetes Mellitus and Cardiovascular Disease in a Managed Care Environment

T. Jeffrey White,[1] *Ann Vanderplas*,[1] *Eunice Chang*,[1] *Christopher M. Dezii*[2] and *Geoffrey D. Abrams*[1]

1 Prescription Solutions®, Costa Mesa, California, USA
2 Bristol-Myers Medical Affairs, Plainsboro, New Jersey, USA

Abstract

Objective: To assess the relationship between diabetic medication adherence, total healthcare costs, and utilization within patients with type 2 diabetes mellitus and concomitant diabetes and cardiovascular disease (CVD).

Research design and methods: This study was a retrospective analysis of pharmacy and medical claims from 1 April 1998 through 31 March 2000 within a managed care organization's database. Patients were identified who had received an oral antihyperglycemic medication or had a diagnosis of CVD, were continuously enrolled in the health plan, and were ≥30 years of age. The likelihood of an emergency room (ER) or hospital admission and total healthcare costs related to all causes, stratified by antihyperglycemic medication adherence cohort within the diabetes only and diabetes + CVD groups, were examined over 360 days from the date the patient was identified.

Results: For diabetes patients with ≤75, >75 to ≤95, and >95% adherence, adjusted total healthcare costs (from April 1998 to March 2000) were $US5706, $US5314, and $US4835, respectively ($p < 0.001$). Patients with ≤75 and >75 to ≤95% adherence had a 31% and 19% greater chance of a hospital/ER admission than those in the >95% cohort, respectively. Adjusted healthcare costs (from April 1998 to March 2000) for those with ≤75, >75 to ≤95, and >95% adherence within the diabetes + CVD cohort was $US37 648, $US31 547, and $US25 354 ($p < 0.001$). Patients who were ≤75 and >75 to ≤95% adherent had a 44% and 51% greater chance of a hospital/ER admission than those with >95% adherence, respectively.

Conclusions: Higher adherence to oral antihyperglycemic agents is associated with lower healthcare resource utilization and costs for patients with diabetes only and patients with concomitant diabetes and CVD.

Approximately 17 million people, or 6.2% of the US population, have diabetes mellitus.[1] The disease is the fifth-leading cause of death in the US, costing $US98 billion annually in direct and indirect expenditures.[2] Cardiovascular disease (CVD) is the most costly, as well as the most prevalent, complication of diabetes. In 1997, CVD was responsible for $US7 billion of the $US44.1 billion spent on direct medical costs for diabetes.[2,3] These costs are attributable to the increased morbidity and mortality associated with concomitant diagnoses of the two conditions.[4,5] Approximately 65% of all patients with diabetes will die because of CVD and stroke, with the cumulative lifetime incidence of cardiovascular mortality associated with diabetes being 30–54% for type 1 and 38–41% for type 2 diabetes.[4,6]

Literature-based evidence suggests that having both diabetes and CVD will lead to greater adverse outcomes compared with diabetes or CVD alone.[7-12] Despite significant improvements in

short-term coronary care, diabetes patients with acute myocardial infarction (MI) still have a high mortality rate. One study, however, demonstrated that diabetic patients with acute MI had better survival rates after 1 year of tight glucose control compared with patients receiving conventional therapy.[13] Furthermore, studies measuring direct medical costs associated with MI in patients with diabetes versus patients without diabetes also demonstrated that dual diagnoses was associated with higher medical costs.[14] For example, the direct cost of MI in a patient without diabetes is $US18 577, whereas for a patient with concomitant diabetes the direct cost is $US26 414.[6] These cost differences demonstrate the need for treatment 'effectiveness' evaluation in this specific patient population. The results of this study will assist both patients and healthcare professionals in determining the role medication adherence plays in improving health outcomes, as well as controlling healthcare costs for diabetes and cardiovascular disease patients.

Research Design and Methods

This was a retrospective database analysis of pharmacy and medical claims from a large California-based managed care organization. The identification period was between 1 April 1998 and 31 March 1999. Members included in the cohorts were either patients who had a claim for an oral antihyperglycemic medication prescription or whose claims history contained in the International Classification of Diseases (9th edition) [ICD-9][15] diagnosis code for CVD during the identification period. Pharmacy claims were used to identify patients with diabetes since this is the only indication for these medications. The ICD-9 diagnosis codes were used to identify the CVD cohort since CVD medications can have multiple indications. All patients who fulfilled the criteria were examined; not just those newly diagnosed or newly initiated on therapy. The date of diagnosis of CVD or of first antihyperglycemic prescription fill in the identification period was marked as the index date, from which each patient was followed for 360 days (follow-up period). Prescriptions for type 2 diabetes included alpha-glucosidase inhibitors, biguanides, meglitinides, sulfonylureas, thiazolidinediones, and combination therapy. The analysis excluded patients who were <30 years old or were not continuously enrolled in the health plan for 360 days after the index date. Patients using insulin were included in the study, as long as they received an oral antihyperglycemic medication as their primary course of therapy. Since adherence to insulin is not adequately measurable using claims data, adherence measurements were limited to oral antihyperglycemic therapy.

Patients were stratified into the diabetes only cohort if they received an oral antihyperglycemic medication and did not have a diagnosis of CVD at any time during their follow-up. Patients were stratified into the diabetes + CVD cohort if they received any oral antihyperglycemic medication in addition to having a diagnosis of CVD during the follow-up period. Patients in the diabetes + CVD and diabetes cohorts were mutually exclusive.

For each cohort, baseline demographic data at the index date is provided. In addition, healthcare utilization and costs for all causes were calculated for the follow-up period. The costs of all medications, medical claim costs (which included hospitalizations, emergency room [ER] visits, procedures, and physician and other professional interventions), and total costs (pharmacy and medical cost) were calculated. Hospital length of stay was calculated based on admission and discharge dates of each hospitalization.

The diabetes only and diabetes + CVD cohorts were further stratified by adherence categories. Statistical analyses were performed within the diabetes only and diabetes + CVD cohorts across adherence categories.

A weighted adherence was calculated for oral antihyperglycemic medications used during the follow-up period. A medication possession ratio (MPR) was first calculated as the total days' supply of oral antihyperglycemic therapy, received during the post-index period divided by the number of days of therapy between the first fill and last fill of the oral antihyperglycemic medication, plus the days' supply of the last fill. An MPR was determined for each time segment. In order to take into account that multiple medications could have been taken at the same time, the average MPR was calculated for concurrent medications for each time segment. The weight of each time segment was calculated as the proportion of time segment out of the total follow-up period. Finally, the weighted adherence was calculated as the sum of the MPR for each time segment multiplied by its associated weight. The weighted adherence was truncated to 1.0.

The adherence rate cut points used to create the adherence categories were ≤75%, >75% to ≤95%, and >95% and were selected based on the distribution of the data. Adherence to CVD medication was not addressed, because the objective of this study was to determine the relationship between oral antihyperglycemic adherence and healthcare costs and utilization.

To compare health costs, multivariate analyses of adjusted costs were performed, adjusting for age, sex, and Charlson Comorbidity Index (CCI). An adapted version[16] of the clinical index developed by Charlson and colleagues, which is based on the ICD-9 codes, was utilized in this study. This index contains 17 diagnostic categories, each having an associated weight based on adjusted risk of 1-year mortality. The overall score reflects the cumulative increased likelihood of 1-year mortality. The higher the score, the more severe the burden of comorbidity. Least-square means are

Table I. Baseline characteristics of patients with diabetes mellitus taking oral antihyperglycemic medications in a retrospective analysis of pharmacy and medical claims from 1 April 1998 to 31 March 2000 within a managed care organisation

	Cohort		Total patients	p-Value[a]
	DM	DM + CVD		
Member count (%)	50 957 (76.02)	16 072 (23.98)	67 029 (100.0)	
Mean age at index [years (SD)]	64.32 (12.78)	71.74 (9.46)	66.10 (12.48)	<0.001
Number of patients who were male (%)	25 549 (50.14)	9114 (56.71)	34 663 (51.71)	<0.001
Number of patients enrolled in healthcare plan (% of patients in each cohort)				
commercial	18 855 (37.00)	2062 (12.83)	20 917 (31.21)	<0.001
Medicare + choice	32 102 (63.00)	14 010 (87.17)	46 112 (68.79)	
Number of patients who had insulin at any time during the study (%)	5310 (10.42)	2911 (18.11)	8221 (12.26)	<0.001
Mean Charlson Comorbidity Index score (SD)	1.48 (1.17)	3.28 (1.88)	1.91 (1.57)	<0.001
Mean Charlson Comorbidity Index score excluding DM and CVD comorbidities (SD)	0.34 (1.04)	0.87 (1.57)	0.47 (1.21)	<0.001

a A comparison of DM vs DM + CVD groups.

CVD = cardiovascular disease; **DM** = diabetes mellitus; **SD** = standard deviation.

reported with 95% confidence intervals. Influential outliers were checked for in each of the cost data analyses.

Logistic regression was performed to determine the risk of having an ER or hospital visit with varying levels of medication adherence. This model also adjusted for age, gender, and CCI. For both the multivariate analyses of adjusted health costs and logistic regression of risk of having an ER or hospital visit, interaction terms were checked and included where significance was found. All reported p-values are two-sided using an alpha level of 0.05 for comparison. SAS® v8.1 was used for all data manipulation and statistical analyses.

Results

Study Cohort Characteristics

Out of a total of 67 029 patients who were included in the study, 50 957 (76.02%) had diabetes only, and 16 072 patients (23.98%) had diabetes + CVD (table I). The mean age was 66.10 years (± 12.48), with 51.71% of the patients being male. Approximately 69% were enrolled in Medicare plus Choice while 31% were commercial members of the healthcare plan. The mean CCI was 1.91 (± 1.57), or 0.47 excluding diabetes and CVD comorbidities, and 12.26% of patients from the diabetes only and diabetes + CVD cohorts were also using insulin at the index date.

The diabetes + CVD cohort was significantly older than the diabetes only cohort (71.74 versus 64.32 years; $p < 0.001$). However, patients in the diabetes + CVD group had a higher average CCI (indicating a more severe burden) compared with the diabetes only cohort (3.28 versus 1.48; $p < 0.001$). Excluding diabetes and CVD comorbidities, the diabetes + CVD cohort continued to have a higher mean CCI (0.87 versus 0.34; $p < 0.001$).

Descriptive Healthcare Utilization and Cost

Overall, adherence with oral antihyperglycemic medication was 0.78 (table II). During the 1-year follow-up period, all patients had an average of 8.93 (± 9.25) outpatient visits, 0.34 (± 0.98) ER visits, and 1.13 (± 3.86) hospitalizations, with a mean hospital stay of 1.06 days (± 4.68). The patients' mean total healthcare costs were $US11 354 (± $US36 023).

Among the study cohorts, patients with diabetes only and those with diabetes + CVD had a mean of 7.36 and 13.92 outpatient visits, respectively ($p < 0.001$). The diabetes only and diabetes + CVD cohorts incurred an average of 0.18 and 0.84 ER visits, respectively ($p < 0.001$) with a mean of 0.44 and 3.31 hospital admissions, respectively ($p < 0.001$). In addition, mean length of stay for patients in the diabetes only and those with diabetes + CVD cohorts were 0.35 and 3.31 days ($p < 0.001$), with mean total healthcare costs of $US5215 and $US30 816 ($p < 0.001$), respectively. No influential outliers were found for any of the cost data analyses.

Adherence Cohort Analyses

Among the diabetes cohort, 16 713 (32.80%), 14 074 (27.62%), and 20 170 (39.58%) were stratified into the ≤75, >75 to ≤95, and >95% adherence categories, respectively (table III). Patients who were >95% adherent with their oral antihyperg-

Table II. Clinical outcomes of diabetic patients taking oral antihyperglycemic medications in a retrospective analysis of pharmacy and medical claims from 1 April 1998 to 31 March 2000 within a managed care organisation

	Cohort		Total patients	p-Value[a]
	DM (n = 50 957)	DM + CVD (n = 16 072)	(n = 67 029)	
Mean adherence [SD (%)]	0.78 (0.26)	0.79 (0.26)	0.78 (0.26)	0.58
Mean number of outpatients visits (SD)	7.36 (7.81)	13.92 (11.43)	8.93 (9.25)	<0.001
Number of patients who had an ER visit/ hospitalization during follow-up (% of patients from each cohort)	10 343 (20.30)	9903 (61.62)	20 246 (30.20)	<0.001
Mean number of ER visits (SD)	0.18 (0.60)	0.84 (1.59)	0.34 (0.98)	<0.001
Mean number of hospital visits (SD)	0.44 (2.01)	3.31 (6.56)	1.13 (3.86)	<0.001
Mean total number of hospital days (SD)	0.35 (2.28)	3.31 (8.26)	1.06 (4.68)	<0.001
Mean pharmacy costs [SD ($US)]	1125 (1183)	1709 (1419)	1265 (1269)	<0.001
Mean non-pharmacy costs [SD ($US)]	4090 (18 835)	29 108 (61 297)	10 089 (35 842)	<0.001
Mean total costs [SD ($US)]	5215 (18 990)	30 816 (61 404)	11 354 (36 023)	<0.001

a A comparison of DM vs DM + CVD groups.

CVD = cardiovascular disease; **DM** = diabetes mellitus; **ER** = emergency room; **SD** = standard deviation.

lycemic medications tended to be older (mean age 66.66 years) than those who were ≤75, or >75 to ≤95% adherent (mean age 61.64 and 64.13 years, respectively; $p < 0.001$). Although statistically significant ($p = 0.05$), the proportion of males and females across adherence categories within the diabetes only cohort was similar. CCI was not statistically different among the three adherence categories in the diabetes only cohort. However, patients who were ≤75% adherent (in the diabetes only cohort) had the highest proportion of insulin use during the follow-up period as compared with the >75% to ≤95% and >95% cohorts (13.33% versus 9.24% versus 8.83%, respectively; $p < 0.001$).

Summarizing the healthcare utilization for patients in the diabetes only cohort, those who were >95% adherent incurred more outpatient visits (7.74) than those in the ≤75% and >75 to ≤95% categories (6.90 and 7.36, respectively; $p < 0.001$), while those who were ≤75% adherent with their oral antihyperglycemic medications had a higher average number of ER visits (0.21 versus 0.18 versus 0.15; $p < 0.001$) and hospitalizations (0.53 versus 0.43 versus 0.36; $p < 0.001$) in addition to a longer mean length of hospital stay (0.47 versus 0.38 versus 0.23 days; $p < 0.001$) [table IV]. Mean unadjusted pharmacy costs were highest for patients who were >95% adherent ($US1402) versus <75% adherent and >75 to ≤95% adherent ($US766 and $US1153, respectively; $p < 0.001$) whereas mean total costs were highest for patients who were ≤75% adherent with their oral antihyperglycemic medications ($US5605) versus >75 to ≤95% adherent and >95% adherent ($US5333 and $US4809, respectively; $p < 0.001$).

Adjusting for the main effects of age, sex, and CCI, mean adjusted pharmacy costs were highest for patients who were >95% adherent while adjusted non-pharmacy and total costs were greatest for the least adherent cohort ($p < 0.001$) [table V].

Adjusted results from the logistic regression analysis showed that within the diabetes only cohort, patients who were >75 to ≤95% adherent were at a 1.19 (95% CI 1.12, 1.26) increased risk of having an ER or hospital admission compared with those who were >95% adherent, while patients who were ≤75% adherent, had a 1.31 (95% CI 1.24, 1.38) increased risk of being admitted to the ER or hospital (figure 1).

Among the diabetes + CVD cohort, 5217 (32.46%), 4445 (27.66%), and 6410 (39.88%) were included in the ≤75, >75 to ≤95%, and >95% adherence categories, respectively (table III). Similar to the diabetes cohort, patients within the diabetes + CVD group who were >95% adherent with their oral antihyperglycemic medications tended to be older than those who were ≤75, or >75 to ≤95% adherent (mean age 72.07, 71.41 and 71.63 years, respectively; $p < 0.001$). The >95% adherent category had the highest proportion of males, followed by the >75 to ≤95 and ≤75% adherent cohorts (58.30% versus 56.15% versus 55.22%; $p = 0.003$). Among the ≤75, >75 to ≤95, and >95% adherence cohorts, patients who were ≤75% adherent with their oral antihyperglycemic medications had the highest mean CCI (3.53 versus 3.28 versus 3.09; $p < 0.001$) as well as the highest proportion of insulin use during the follow-up period (22.85% versus 16.65% versus 15.27%; $p < 0.001$).

Between the ≤75, >75 to ≤95%, and >95% adherence groups of the diabetes + CVD cohort, patients who were ≤75% adherent with their oral antihyperglycemic medications incurred a higher mean number of outpatient visits (14.39 versus 13.73 versus 13.66; p =

0.001), ER visits (1.10 versus 0.85 versus 0.63; $p < 0.001$), and hospitalizations (4.45 versus 3.39 versus 2.31; $p < 0.001$), and had a longer mean length of hospital stay (4.55 versus 3.51 versus 2.17 days; $p < 0.001$) [table IV]. Average unadjusted pharmacy costs were highest for patients who were >95% adherent ($US1984) versus the ≤75% adherent and >75 to ≤95% adherent groups ($US1355 and $US1727, respectively; $p < 0.001$), however, mean unadjusted total costs were greatest for patients who were ≤75% adherent with their oral antihyperglycemic medications ($US40 126) versus the >75 to ≤95% and >95% adherent groups ($US31 281 and $US22 917, respectively; $p < 0.001$) [table IV].

Similar to the diabetes only cohort, mean adjusted medication costs for the diabetes + CVD cohort was greatest in those who were the most adherent, while non-pharmacy and total costs were highest for those who were least adherent ($p < 0.001$) [table V]. Using the same logistic regression technique, patients who were >75 to ≤95% adherent were at a 1.51 (95% CI 1.39, 1.63) increased risk of having an ER or hospital admission compared with those who were >95% adherent with their oral antihyperglycemic medication, while patients who were ≤75% adherent had a 1.44 (95% CI 1.32, 1.56) increased risk of being admitted to the ER or hospital (figure 1).

Discussion

The results of this investigation suggest that antihyperglycemic medication adherence is associated with lower total healthcare costs and improved patient outcomes in patients with diabetes only and diabetes + CVD. This is consistent with previously published literature that has shown that poor glycemic control, which may result from non-adherence with antidiabetic medications, can result in an increased incidence of complications, leading to increased ER visits and hospitalizations.[5] The mean total cost in the study population was approximately $US11 000 over a 1-year period, which is expected for this age group. As expected, increased healthcare utilization led to higher healthcare-related costs. Although patients who were >95% adherent incurred higher pharmacy costs in both the diabetes only and diabetes + CVD cohorts as compared with those ≤95% adherent, medical costs and total healthcare costs were lower.

In both the diabetes only and diabetes + CVD cohorts, patients who were >95% adherent were older than the other adherence categories. This finding was somewhat consistent with the existing literature.[17-19] However, adherence in elderly patients are of a particular concern because of their common deficits in physical dexterity, cognitive skills, memory, and the number of medications that they are typically prescribed.[20-22] The improvement in adherence in elderly patients observed in this analysis may have

Table III. Baseline characteristics of patients with diabetes mellitus taking oral antihyperglycemic medications according to treatment adherence in a retrospective analysis of pharmacy and medical claims from 1 April 1998 to 31 March 2000 within a managed care organisation

	DM only cohort				DM + CVD cohort			
	adherence to oral antihyperglycemic indicators			p-Value[a]	adherence to oral antihyperglycemic medications			p-Value[b]
	≤75% (n = 16 713)	>75% to ≤95 (n = 14 047)	>95% (n = 20 170)		≤75% (n = 5217)	>75% to ≤95 (n = 4445)	>95% (n = 6410)	
Member count (%)	16 713 (32.80)	14 074 (27.62)	20 170 (39.58)		5217 (32.46)	4445 (27.66)	6410 (39.88)	
Mean age at index (SD) [years]	61.64 (13.95)	64.13 (12.67)	66.66 (11.30)	<0.001	71.41 (10.08)	71.63 (9.44)	72.07 (8.92)	<0.001
Number of patients who were male (%)	8487 (50.78)	7076 (50.28)	9986 (49.51)	0.05	2881 (55.22)	2496 (56.15)	3737 (58.30)	0.003
Mean Charlson Comorbidity Index score (SD)	1.48 (1.20)	1.49 (1.20)	1.47 (1.13)	0.31	3.53 (2.08)	3.28 (1.86)	3.09 (1.69)	<0.001
Mean Charlson Comorbidity Index score excluding DM and CVD comorbidities (SD)	0.35 (1.08)	0.34 (1.06)	0.33 (0.99)	0.102	1.04 (1.71)	0.87 (1.59)	0.72 (1.43)	<0.001

a Comparison of three adherence categories within the DM only cohort.

b Comparison of three adherence categories within the DM + CVD cohort.

CVD = cardiovascular disease; **DM** = diabetes mellitus; **SD** = standard deviation.

been attributable to the duration of their diagnosis of diabetes or diabetes + CVD, adjustment to treatment regimen or lifestyle changes, and higher awareness of complications associated with diabetes. In addition, patients who were ≤75% adherent were more likely to use insulin in both cohorts. Patients who are not adherent with their oral antihyperglycemic medications are more likely to require insulin to achieve glycemic control.

Relative risk calculations also indicated that patients who were ≤75% adherent had more ER and hospital admissions compared with patients who were >75% adherent. However, results did indicate that patients in the >75 to ≤95% adherence group of the diabetes + CVD cohort had a higher risk of ER or hospital admission than those in the ≤75% adherence cohort. While this may seem unlikely, many of the patients in the least adherent group might have had more serious complications relating to CVD rather than diabetes. This would have allowed these patients to be less adherent with their oral antihyperglycemic medication, without experiencing significant diabetes-related illnesses. The higher CCI score for this cohort may be attributable to increased CVD complications rather than complications relating to antihyperglycemic medication non-adherence among this group. Additionally, members who were >75 to ≤95% adherent might have experienced greater fluctuation in their blood glucose levels, leading to increased ER and hospital admissions.

It has been reported that the most important cost factor for patients with diabetes relates to the chronic complications of diabetes as the disease progresses. Because of this, therapeutic interventions should aim at preventing costly complications. It has been shown that CVD is common and is the leading cause of mortality in persons with type 2 diabetes.[23] The Diabetes Control and Complications Trial suggests that there may be important effects of intensive diabetes treatment on the development of macrovascular disease.[24] In addition, there is a strong epidemiologic association between poorly controlled hyperglycemia and increased rates of CVD; therefore, maintaining good glycemic control by being adherent with diabetic medications could decrease the risk of CVD.

There are several issues to consider when interpreting the findings of this study. Since this was not a large randomized, controlled study, but rather a retrospective database analysis of

Table IV. Clinical outcomes of patients with diabetes mellitus taking oral antihyperglycemic medications according to treatment adherence in a retrospective analysis of pharmacy and medical claims from 1 April 1998 to 31 March 2000 within a managed care organisation

	DM only cohort				DM + CVD cohort			
	adherence to oral antihyperglycemic medications			p-Value[a]	adherence to oral antihyperglycemic medications			p-Value[b]
	≤75%) (n = 16 713)	>75 to ≤95% (n = 14 074)	>95% (n = 20 170)		≤75% (n = 5217)	>75% to ≤95% (n = 4445)	>95% (n = 6410)	
Mean adherence (SD)	0.46 (0.21)	0.87 (0.06)	0.99 (0.01)	<0.001	0.46 (0.21)	0.87 (0.05)	0.99 (0.01)	<0.001
Mean number of outpatients visits (SD)	6.90 (7.87)	7.36 (7.86)	7.74 (7.69)	<0.001	14.39 (12.51)	13.73 (11.12)	13.66 (10.69)	0.001
Had an ER/ hospitalization during follow-up (%)	3680 (22.02)	2938 (20.88)	3725 (18.47)	<0.001	3512 (67.32)	2868 (64.52)	3523 (54.96)	<0.001
Mean number of ER visits (SD)	0.21 (0.74)	0.58 (0.43)	0.49 (0.36)	<0.001	1.10 (2.03)	0.85 (1.46)	0.63 (1.19)	<0.001
Mean number of hospital visits (SD)	0.53 (2.47)	0.43 (1.84)	0.36 (1.68)	<0.001	4.45 (8.52)	3.39 (6.06)	2.31 (4.62)	<0.001
Mean total number of hospital days (SD)	0.47 (3.01)	0.38 (2.25)	0.23 (1.46)	<0.001	4.55 (10.64)	3.51 (7.90)	2.17 (5.76)	<0.001
Mean pharmacy costs ($US) [SD]	766 (1031)	1153 (1122)	1402 (1262)	<0.001	1355 (1274)	1727 (1356)	1984 (1509)	<0.001
Mean non-pharmacy costs ($US) [SD]	4839 (27 445)	4180 (14 697)	3407 (10 980)	<0.001	38 771 (84 703)	29 555 (51 562)	20 933 (39 952)	<0.001
Mean total costs ($US) [SD]	5605 (27 628)	5333 (14 855)	4809 (11 152)	<0.001	40 126 (84 858)	31 281 (51 693)	22 917 (40 105)	<0.001

a Comparison of three adherence categories within the DM only cohort.

b Comparison of three adherence categories within the DM + CVD cohort.

CVD = cardiovascular disease; **DM** = diabetes mellitus; **ER** = emergency room; **SD** = standard deviation.

Table V. Adjusted healthcare costs for patients with diabetes taking oral antihyperglycemic medications according to treatment adherence in a retrospective analysis of pharmacy and medical claims from 1 April 1998 to 31 March 2000 within a managed care organization

Economic costs ($US)[a]	Adherence to oral antihyperglycemic medications			p-Value
	≤75%	>75% to ≤95	>95%	
DM only cohort				
Mean pharmacy costs (95% CI)	762 (745, 779)	1157 (1138, 1175)	1429 (1413, 1444)	<0.001
Mean non-pharmacy costs (95% CI)	4944 (4667, 5220)	4157 (3858, 4456)	3406 (3155, 3658)	<0.001
Mean total costs (95% CI)	5706 (5428, 5984)	5314 (5013, 5614)	4835 (4582, 5088)	<0.001
DM + CVD cohort				
Mean pharmacy costs (95% CI)	1317 (1280, 1353)	1732 (1692, 1771)	2027 (1994, 2060)	<0.001
Mean non-pharmacy costs (95% CI)	36 332 (34 776, 37 887)	29 815 (28 137, 31 492)	23 326 (21 925, 24 728)	<0.001
Mean total costs (95% CI)	37 648 (36 091, 39 205)	31 547 (29 868, 33 226)	25 354 (23 951, 26 757)	<0.001

a Adjusted for age at index, sex, and Charlson Comorbidity Index.

CI = confidence interval; **CVD** = cardiovascular disease; **DM** = diabetes mellitus.

pharmacy and medical claims, a causal relationship between non-adherence and higher utilization and healthcare cost cannot be established. Furthermore, it was not determined that non-adherence preceded the outcome measures (utilization and total healthcare cost). For example, we cannot conclude that antihyperglycemic non-adherence causes more hospitalizations compared with higher adherence. Nevertheless, it can be concluded that there is at least an association between non-adherence and higher utilization and total healthcare cost in the diabetes only and diabetes + CVD populations.

Another consideration is that study patients were not newly diagnosed with diabetes (or CVD). Utilization from complications of diabetes may be due to disease progression and associated comorbidities. Additionally, patients' lifestyle differences, such as smoking, poor diet, and physical inactivity, which were not identifiable in this study, could have contributed to increased utilization and cost, independent of adherence. There may have been interventional programs, which may have occurred during the time of the study that may have influenced the outcomes. Furthermore, claims data may not accurately represent medical-use patterns or pharmacy refill patterns for insulin. In particular, those patients who were identified as receiving an oral-antihyperglycemic medication, but were then switched to insulin only during the follow-up period, were assumed to be non-adherent with their medication because of a lack of fills for their oral medication. Also, since insulin-only users were excluded, the study findings are limited to the oral antihyperglycemic population, which may limit the generalizability of the findings. Despite these limitations, the findings are very valuable from a managed care perspective.

Conclusion

Antihyperglycemic medication adherence plays a major role in lowering the cost associated with diabetes complications. These findings further illustrate the importance of incorporating pharmacy and medical claims data to generate information useful for managed care decision-making. In this case, lower pharmacy utilization (e.g. lower adherence) was associated with higher total healthcare cost. Furthermore, these findings suggest that there is an opportunity for pharmacy benefit managers to implement programs intended to increase medication adherence, since adherence is associated with lower healthcare utilization and cost. Finally, patients and healthcare professionals should be reminded of the importance of adherence not only to oral antihyperglycemic medi-

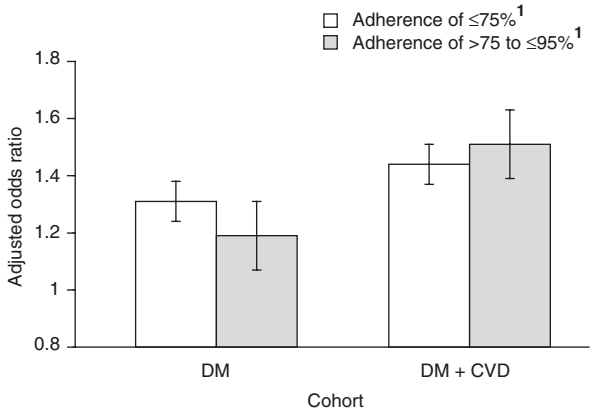

Fig. 1. Adjusted odds ratio estimates and 95% confidence intervals for risk of emergency room/hospital admissions among adherence categories within the type 2 diabetes mellitus (DM) and concomitant DM and cardiovascular disease (DM + CVD) cohorts (adjusted for age at index, sex, and Charlson Comorbidity Index). **1** indicates compared with >95% adherence.

cations, but also to other therapies in general, and how adherence is associated with lower healthcare costs, increased quality of life, and an overall reduction in burden to the healthcare system.

Acknowledgments

Bristol-Myers Squibb Company, Princeton, New Jersey, USA, funded the research described in this manuscript. Researchers from the Pharmacoeconomics and Health Outcomes Research Department of Prescription Solutions, a pharmacy benefit and medical management company, and Bristol-Myers Squibb conducted this study.

References

1. American Diabetes Association. Basic diabetes information [online]. Available from URL: http://www.diabetes.org [Accessed 2002 Aug 30]
2. American Diabetes Association. Economic consequences of diabetes mellitus in the US in 1997. Diabetes Care 1998; 21: 296-309
3. Centers for Disease Control and Prevention. Cardiovascular disease [online]. Available from URL: http://www.cdc.gov/nccdphp/cardiov.htm [Accessed 2002 Aug 16]
4. Gaster B, Hirsch IB. The effects of improved glycemic control on complications in type 2 diabetes. Arch Intern Med 1998; 158: 134-40
5. Smith TL, Melfi CA, Kesterson JA, et al. Direct medical charges associated with myocardial infarction in patients with and without diabetes. Med Care 1999; 37: AS4-11
6. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention: diabetes surveillance report, 1999. Atlanta (GA): US Department of Health and Human Services, 1999
7. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med 1991; 151: 1141-7
8. Seeman T, de Leon CM, Berkman L, et al. Risk factors for coronary heart disease among older men and women: a prospective study of community-dwelling elderly. Am J Epidemiol 1993; 138: 1037-49
9. Pan W, Cedres LB, Liu K, et al. Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. Am J Epidemiol 1986; 123: 504-16
10. Kleinman JC, Donahue RP, Harris MI, et al. Mortality in diabetics in a national sample. Am J Epidemiol 1988; 128: 389-401
11. Barrett-Connor E, Cohn BA, Wingard DL, et al. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. JAMA 1991; 256: 627-31
12. Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. J Am Public Health 1991; 81: 1158-62
13. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995; 26: 57-65
14. Gilmer TP, O'Connor PJ, Manning WG, et al. The cost to health plans of poor glycemic control. Diabetes Care 1997; 20: 1847-53
15. International classification of diseases. 9th ed. Geneva: World Health Organization, 1997
16. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992; 45: 613-9
17. Morrell RW, Park DC, Kidder DP, et al. Adherence to antihypertensive medications across the life span. Gerontologist 1997; 37: 609-17
18. Park DC, Hertzog C, Leventhal H, et al. Medication adherence in rheumatoid arthritis patients: older is wiser. J Am Geriatr Soc 1999; 47: 172-93
19. Raiz LR, Kilty KM, Henry ML, et al. Medication compliance following renal transplantation. Transplantation 1999; 68: 51-5
20. Claesson S, Morrison A, Wertheimer AI, et al. Compliance with prescribed drugs: challenges for the elderly population. Pharm World Sci 1999; 21: 256-9
21. Cramer JA. Enhancing patient compliance in the elderly: role of packaging aids and monitoring. Drugs Aging 1998; 12: 7-15
22. Ennis KJ, Reichard RA. Maximizing drug compliance in the elderly: tips for staying on top of your patients' medication use. Postgrad Med 1997; 102: 211-34
23. Savage P. Cardiovascular complications of diabetes mellitus: what we know and what we need to know about their prevention. Ann Intern Med 1996; 124: 123-6
24. The Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol 1995; 75: 894-903

About the Author: T. Jeffrey White, Pharm.D., M.S., is Director of Clinical Research at Prescription Solutions®. Dr White received his Doctor of Pharmacy degree and Masters of Science in Pharmaceutical Economics and Policy from the University of Southern California. His primary research interest is in quantifying the value of pharmaceuticals with respect to clinical, economic, and humanistic outcomes in real-world settings.

Correspondence and offprints: Dr *T. Jeffrey White*, Prescription Solutions®, 3515 Harbor Boulevard, Mail Stop LC07-264, Costa Mesa, CA 92626, USA. E-mail: information@rxsolutions.com