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Failure to Reach Target Glycated A1c Levels Among Patients with Diabetes Who Are Adherent to Their Antidiabetic Medication

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Abstract

The objectives of this study were to describe patient characteristics and types of medications taken by those with poor glycemic control (A1c > 7%) despite being adherent to antidiabetic medications. This is a retrospective analysis of administrative data from adult patients with diabetes enrolled in a large health plan in Hawaii (n = 21,267 observations for 11,013 individuals) and adherent to their antidiabetic medications. Multivariable logistic regressions were estimated to determine characteristics and types of medications associated with poor glycemic control. Separate models were estimated to examine category of medication (insulin only, 1 oral medication, multiple oral medications, both oral medications and insulin) and specific therapeutic class of oral antidiabetic medications. Despite being adherent to their medications, 56.1% of patients had poor glycemic control. Compared to patients taking combination sulfonylureas, patients had a higher odds of having A1c > 7% for all other oral diabetic medications, with odds ratios ranging from OR = 2.07 for sulfonylureas alone to OR = 1.33 for combination DPP-4 inhibitors. More than half of patients in this study had poor A1c control despite being adherent to their medications. This suggests that physicians, pharmacists, and other providers may need to monitor treatment regimens more carefully, encourage healthy behaviors, and intensify pharmacological treatment as needed. (*Population Health Management* 2014;17:218–223)

Estimates from the International Diabetes Federation suggest that 371 million people in the world have diabetes and that, by 2030, this will increase to 552 million people.[1] Diabetes affects morbidity and mortality and also has an economic impact. In the United States, diabetes has been estimated to result in $245 billion in health care expenditures.[2]

Diabetes is a chronic disease that requires continued pharmacological and nonpharmacological management to prevent complications such as cardiovascular disease, retinopathy, nephropathy, and neuropathy.[3,4] Although it is well known that antidiabetic pharmacotherapies significantly reduce the risk of adverse events in patients with diabetes, medication adherence is key to realizing the full potential effect of these treatments.[5] Despite this knowledge, adherence to recommended medications is known to be low, ranging from 67%–85%.[6–12]

Lowering hemoglobin A1c (A1c) to 7% has been shown to reduce microvascular complications.[13,14] Current American Diabetes Association guidelines define an A1c < 7% as a reasonable goal for most adults.[15] However, even when patients adhere to their recommended medication regimens they still may not achieve these targeted A1c levels. Reasons may include severity of disease, dosage prescribed, and overall efficacy of the chosen medication. Although many studies have focused on factors affecting medication adherence, to the study team's knowledge, none has examined factors related to achieving glycemic control among patients who are adherent to medication.

The goals of this study were to estimate the percentage of patients with diabetes who fail to achieve target A1c levels despite being adherent to medication, and to describe characteristics of patients and types of medications taken by those who are adherent to medication but do not reach target goals.

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Methods

The study team conducted a retrospective analysis of administrative data (2008–2010) from adult patients with diabetes who were enrolled in a large health plan in Hawaii (n = 21,267 observations for 11,013 individuals). To be included, patients needed to meet the following criteria: (1) be identified as having diabetes using algorithms employed by disease management programs; (2) be at least 18 years old; (3) be enrolled with medical and drug coverage; (4) have A1c measured at least once during the year; (5) be adherent to the medication (ie, proportion of days covered [PDC] ≥ 80%); (6) have at least 2 years of data including A1c lab values so that the study team could adjust for prior year's A1c level. Gestational diabetes was excluded. Disease management algorithms were also used to identify patients with diabetes, coronary artery disease, and congestive heart failure.

Patient information including age, sex, duration of diabetes, and morbidity level was obtained from administrative data. Patient morbidity level was determined by using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes according to the Johns Hopkins Adjusted Clinical Group methodology[16]; levels of 4 or 5 on the 5-point scale were considered high morbidity. Diabetes duration was calculated as years since first diagnosis of diabetes in the health plan's administrative data and was broken into categories (1–2 years; 3–4 years; 5–9 years; 10+ years). The prior year's A1c was categorized as <7%, 7%–9%, or >9%.

Data on race/ethnicity were available for 44% of patients from annual membership surveys. Members were asked to check all race/ethnicities that applied. Those who selected more than 1 race/ethnicity were classified as ''mixed race'' ($n = 1456$). The exception was Native Hawaiians. In keeping with Hawai'i State Department of Health classifications, Native Hawaiian were categorized as anyone who checked Hawaiian even if they checked more than 1 race/ethnicity. Racial/ethnic categories for this study included the 6 largest groups: white, Filipino, Japanese, Chinese, Native Hawaiian, and other Pacific Islander.

Medication use

Medications were grouped into the following 6 specific therapeutic classes: (1) insulins; (2) DPP-4 inhibitors (eg, sitagliptin, saxagliptin); (3) GLP-1 receptor agonists (eg, exenatide, liraglutide); (4) Sulfonylureas (eg, chlorpropamide, glipizide); (5) combinations with sulfonylureas (eg, metformin HCL); (6) combinations with DPP-4 inhibitors (eg, metformin and sitagliptin). Amylin analogs were dropped because of low utilization. For the initial model, medication use was categorized into 4 categories: (1) insulin use only; (2) 1 oral medication; (3) multiple oral medications; (4) oral medications and insulin. For the second model, the sample was restricted to patients not on insulin and included indicators for all types of oral medications taken in a given year.

Medication adherence

Prescription data on medication names, fills, and days of supply were obtained from pharmacy claims databases. PDC was used to estimate medication adherence for antidiabetic medications:

$$\frac{\textit{Number of days in period ''covered'' by medication}}{\textit{Number of days of drug enrollment}}$$

PDC is a well-validated and widely used measure of medication adherence.[17,18] A patient's measurement period was determined as the first prescription date in a given year through the end of that calendar year or until date of disenrollment. Within the measurement period, the study team counted days the patient was covered by at least 1 drug for each type of medication based on prescription fill date and days of supply. Number of covered days was divided by number of days of drug coverage to obtain PDC. Only patients with a PDC >80% were included.

Statistical analyses

For the main analyses, among patients who are adherent to their antidiabetic medications, multivariable logistic regression analysis was used to examine patient characteristics and type of medication related to achievement of target A1c levels. The model adjusted for age, sex, history of cardiovascular disease, ethnicity, morbidity level, duration of diabetes, prior year's A1c level, and year. The University of Hawaii Committee on Human Studies approved this study as exempt. All analyses were conducted using Stata statistical software, release 11.0 (StataCorp LP, College Station, TX).

Results

Patient characteristics and medication regimen

Despite being adherent to their medications, 56.1% of patients had poor glycemic control. Mean age of those reaching goal was several years older than for those not reaching goal ($P < 0.001$, Table 1). A higher portion of patients were female and had high morbidity among those ''at goal'' compared to the ''not at goal'' group. History of cardiovascular disease did not differ significantly with A1c level but race/ethnicity did, with a higher percentage of Native Hawaiians in the ''not at goal'' group than in the ''at goal'' group. Longer duration of diabetes also was significantly associated with poor control.

Type of medication also differed significantly according to A1c level (Table 2). In terms of category of medication regimen, more than half of those in control were on insulin only compared to approximately one quarter of those out of control. Approximately 44% of those out of control were on only a single oral medication, compared to a third of those in control.

Category of medication regimen

Compared to taking insulin alone, taking both insulin and oral medications was associated with poor A1c control (odds ratio [OR] = 1.32), while taking oral medications only was associated with better control, after adjustment for other factors (Table 3).

Patients aged 50 to 64 were less likely to have poor A1c control than patients aged 35 to 49, but more likely than patients in the 65 and older age group (Table 3). High morbidity score also was associated with lower A1c levels,

Table 1. Patient Characteristics Related to Getting to Goal for HbA1c Among Patients Adherent to Medication Regimen

Characteristic	*HbA1c ≤ 7%*	*HbA1c > 7%*	P *value*
Age (years, SD)	63.1 (SD = 11.8)	59.8 (SD = 11.9)	< 0.001
Female (%)	49.8 %	46.5 %	0.003
Coronary artery disease (%)	23.7 %	25.1 %	0.15
Congestive heart failure (%)	10.9 %	11.5 %	0.40
High morbidity (%)	41.1 %	38.5 %	0.01
Race/ethnicity (%)			0.001
White	4.6 %	3.7 %	
Japanese	22.9 %	19.6 %	
Chinese	3.9 %	2.8 %	
Filipino	8.9 %	8.0 %	
Native Hawaiian	6.8 %	8.2 %	
Other Pacific Islanders	0.3 %	0.4 %	
Mixed race	3.9 %	3.9 %	
Other race	2.1 %	1.4 %	
Race missing	46.4 %	51.9 %	
Diabetes duration			< 0.001
1–2 years	1.9 %	1.2 %	
3–4 years	21.2 %	13.4 %	
5–9 years	42.3 %	37.4 %	
10+ years	34.6 %	48.0 %	

SD, standard deviation.

while having a history of coronary artery disease was associated with higher A1c levels. Shorter duration of diabetes was significantly associated with a decreased odds of poor control (Table 3).

The previous year's A1c level also was strongly and significantly associated with control. As shown in Table 3, patients with an A1c greater than 9% in the prior year and those with a prior year's A1c between 7% and 9% were significantly more likely to be in poor control compared to patients whose A1c in the prior year was less than 7%.

Filipinos and Native Hawaiians were significantly more likely to have poor control than whites after adjustment for other factors (Table 3).

Specific therapeutic class of oral medication

Compared to patients taking combination sulfonylureas, patients had a higher odds of having A1c > 7% for all other oral diabetic medications, with odds ratios ranging from OR = 2.07 for sulfonylureas alone to OR = 1.32 for combination DPP-4 inhibitors (Table 4). The relationships between patient characteristics and having an A1c above goal were similar to those of the previous model, except that race and history of cardiovascular disease were no longer statistically significant.

Discussion

A lot of attention has been focused on developing interventions to improve medication adherence to enable patients to achieve optimal glycemic control. The present study of more than 11,000 insured patients with diabetes found that more than half of patients failed to achieve good glycemic control (A1c < 7%) despite being adherent to their antidiabetic medications. Hence, a focus only on medication adherence may not be enough to reduce the risk of increased

Table 2. Category of Medication and Type of Oral Diabetes Medication Related to Getting to Goal for HbA1c Among Patients Adherent to Their Medication, Unadjusted

	HbA1c ≤ 7%	*HbA1c > 7%*	P *value*
Category of Medication			< 0.001
Insulin only	54.7 %	26.3 %	
Single oral medication only	34.7 %	43.6 %	
Multiple oral medications	3.3 %	7.3 %	
Oral medications and insulin	7.3 %	22.9 %	
Type of oral diabetes medication*			
Combination sulfonylureas	83.5 %	79.7 %	< 0.001
Combination DPP-4 inhibitors	3.6 %	4.9 %	< 0.001
DPP-4 Inhibitors	9.6 %	17.1 %	< 0.001
GLP-1 agonists	2.2 %	5.0 %	< 0.001
Sulfonylureas	38.0 %	55.8 %	< 0.001
Other oral diabetes medications	0.2 %	0.1 %	0.02

*Percentages do not sum to 1 because members can be on more than 1 oral medication.

Table 3. Adjusted Odds Ratio of Poor Glycemic Control (A1c > 7%) Related to Category of Medication and Patient Characteristics (n = 21,267 Observations for 11,013 Individuals)

	Odds Ratio	*95% CI*
Age		
< 35	1.16	[0.79, 1.71]
35–49	1.21	[1.08, 1.36]
50–64	1	
≥ 65	0.86	[0.80, 0.93]
Female	0.98	[0.91, 1.05]
High morbidity	0.89	[0.81, 0.97]
Coronary artery disease	1.11	[1.01, 1.22]
Congestive heart failure	0.96	[0.84, 1.10]
Race/ethnicity		
White	1	
Japanese	1.09	[0.90, 1.32]
Chinese	1.01	[0.77, 1.33]
Filipino	1.28	[1.03, 1.58]
Native Hawaiian	1.25	[1.002, 1.56]
Other Pacific Islander	1.14	[0.62, 2.08]
Other race	0.80	[0.59, 1.09]
Mixed race	1.14	[0.89, 1.46]
Race missing	1.23	[1.02, 1.47]
Study Year		
2008	1	
2009	0.64	[0.59, 0.70]
2010	0.96	[0.88, 1.05]
Diabetes duration		
1–2 years	0.37	[0.22, 0.63]
3–4 years	0.74	[0.66, 0.82]
5–9 years	0.89	[0.82, 0.96]
10+ years	1	
Type of Medication Regimen		
Insulin only	1	
One oral medication	0.37	[0.31, 0.43]
Multiple oral medications	0.71	[0.60, 0.84]
Insulin and oral medications	1.32	[1.10, 1.59]
Prior year's A1C level		
< 7%	1	
7%–9%	8.58	[7.94,9.27]
> 9%	29.1	[24.7,1,34.18]

CI, confidence interval.

Table 4. Adjusted Odds Ratio of Poor Glycemic Control (A1c > 7%) Related to Type of Oral Diabetes Medication and Patient Characteristics (n = 16,524 Observations for 8740 Individuals)

	Odds Ratio	*95% CI*
Age		
< 35	1.81	[1.16, 2.82]
35–49	1.29	[1.14, 1.46]
50–64	1	
≥ 65	0.84	[0.78, 0.92]
Female	1.00	[0.92, 1.08]
High morbidity	0.88	[0.79, 0.97]
Coronary artery disease	1.08	[0.97, 1.20]
Congestive heart failure	0.91	[0.77, 1.06]
Race/ethnicity		
White	1	
Japanese	1.01	[0.81, 1.26]
Chinese	0.88	[0.64, 1.21]
Filipino	1.19	[0.93, 1.51]
Native Hawaiian	1.13	[0.88, 1.46]
Other Pacific Islander	0.88	[0.40, 1.69]
Other race	0.75	[0.51, 1.08]
Mixed race	1.04	[0.78, 1.39]
Race missing	1.11	[0.90, 1.37]
Year		
2008	1	
2009	0.62	[0.57, 0.68]
2010	0.95	[0.86, 1.05]
Diabetes duration		
1–2 years	0.38	[0.21, 0.66]
3–4 years	0.74	[0.66, 0.83]
5–9 years	0.90	[0.82, 0.98]
10+ years	1	
Type of oral medication		
Combination sulfonylureas	1	
Combination DPP-4 inhibitors	1.32	[1.12, 1.57]
DPP-4 Inhibitors	1.54	[1.38, 1.71]
GLP-1 agonists	1.48	[1.21, 1.80]
Sulfonylureas	2.07	[1.92, 2.24]
Other oral diabetes medications	2.56	[0.96, 6.82]
Prior year's A1C level		
< 7%	1	
7%–9%	25.2	[20.8,30.4]
> 9%	8.6	[7.9,9.3]

CI, confidence interval.

morbidity and mortality associated with poor glycemic control. Interventions attempting to improve glycemic control among patients who are adherent will differ from those focused on medication adherence in that they may need to focus less on access to care (in that they have enough access to be adherent to their medication) and more on initial treatment decisions, intensification, and health-related behaviors.

The study found type of medication to be significantly associated with getting to goal among patients who are adherent to medication. Over 46% of patients with diabetes who are adherent to their medication but failed to achieve good glycemic control were on only a single oral medication. This suggests that physicians, pharmacists, and other providers may need to monitor glycemic control more closely and intensify treatment as needed.

However, the study also found that the combination regimen of insulin and oral medications was associated most strongly with suboptimal control, followed by insulin alone, multiple oral medications, and a single oral medication. This is consistent with other findings in the literature.[19,20] This may be because current guidelines recommend starting patients on insulin when their diabetes is not optimally controlled by oral medication. Therefore, patients on insulin may be at a more advanced stage of diabetes at which A1c <7% is more difficult to achieve. Although the study team attempted to adjust for severity of disease by controlling for duration of diabetes, prior year's A1c level, and having cardiovascular disease, there may have been aspects of disease severity not captured in the model. Among oral antidiabetic medications, combination sulfonylureas appeared to be associated with better glycemic control.

The fact that adherence to even the most intensive treatment regimen of combination insulin and oral medications did not achieve A1c goal suggests that emphasis may need

to be placed on nonpharmacological management, such as diet, weight loss, and exercise. Prevention is key in that efforts to reduce obesity and inactivity in younger adults may reduce the incidence of diabetes and may facilitate improved glycemic control among younger adults who have diabetes.[21,22] The findings of a higher odds of suboptimal glycemic control among younger adults is consistent with national data.[23] Promoting better control among younger adults is important in that they are more likely to have a longer duration of diabetes and poor control over a long period of time is associated with a heightened risk of morbidity and mortality.

Also of concern are the higher rates of poor control among Filipinos and Native Hawaiians compared to whites. It is known from previous studies that Filipinos and Pacific Islanders have lower rates of medication adherence than whites.[24,25] To learn that they also have worse glycemic control even when they are adherent to medications suggests the need to develop targeted comprehensive interventions to improve glycemic control that involve improving adherence as well as intensifying treatment as needed and addressing issues related to health behaviors as appropriate.

There are several limitations to this study. First, as with all studies that measure adherence using administrative data, it is not known whether patients actually took their medication, only that they filled their prescriptions. Second, the target A1c level upon which providers and patients have agreed is unknown. There may have been reasons for not setting A1c targets at $<7\%$.[26] Rather, a target level of $\leq 7\%$ was assumed for all patients. Third, this study population included insured patients in a single large health plan in Hawaii, so the results may not generalize to other locations or to uninsured patients. Fourth, information on diet and exercise was not available for this analysis of administrative data. These might be confounding factors that influence glycemic control.

Despite these limitations, the study team believes this study contributes to the literature by focusing on characteristics of patients and types of medications related to poor glycemic control despite being adherent to medications. The study findings suggest that among oral antidiabetic medications, taking combination sulfonylureas may decrease the odds of poor glycemic control. Moreover, as Filipinos, Native Hawaiians, and younger patients may be at increased odds of poor control despite being adherent to medication regimens, special attention may need to be given to their pharmacological and nonpharmacological disease management.

Author Disclosure Statement

Drs. Juarez, Ma, and Davis, Ms Kumasaka, and Mr Shimada declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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