Association of Visit-to-Visit Variability of Hemoglobin A1c and Medication Adherence

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ABSTRACT

BACKGROUND: Medication nonadherence is widespread, but there are few efficient means of detecting medication nonadherence at the point of care. Visit-to-visit variability in clinical biomarkers has shown inconsistent efficiency to predict medication adherence.

OBJECTIVE: To examine the performance of visit-to-visit variability (VTV) of hemoglobin A1c to predict nonadherence to antidiabetic medications.

METHODS: In this cross-sectional study using a clinical and administrative database, adult members of a managed care plan at a safety-net medical center from 2008 to 2012 were included if they had ≥ 3 noninsulin antidiabetic prescription fills within the same class and ≥ 3 A1c measurements between the first and last prescription fills. The independent variable was VTV of A1c (within-subject standard deviation of A1c), and the dependent variable was medication adherence (defined by medication possession ratio) determined from pharmacy claims. Unadjusted and adjusted multivariate logistic regression models were created to examine the relationship between VTV of A1c and medication nonadherence. Receiver-operating characteristic (ROC) curves assessed the performance of the adjusted model at discriminating adherence from nonadherence.

RESULTS: Among 632 eligible subjects, mean A1c was $7.7\% \pm 1.3\%$, and 83% of the sample was nonadherent to antidiabetic medications. Increasing quintiles of VTV of A1c and medication nonadherence were both associated with increased within-subject mean A1c and younger subject age. The logistic regression model (adjusted for age, sex, race/ethnicity, within-subject mean A1c, number of A1c measurements, number of days between the first and last antidiabetic medication prescription fills, and rate of primary care visits during the study period) showed a nonsignificant association of VTV of A1c and medication nonadherence (OR = 1.19, 95% CI = 0.42–3.38 for the highest quintile of VTV). Adding VTV of A1c to a model including age, sex, and race only modestly improved the C-statistic of the ROC curve from 0.6786 to 0.7064.

CONCLUSIONS: VTV of A1c is not a robust predictor of antidiabetic medication nonadherence. Further innovation is needed to develop novel methods of detecting nonadherence.

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What is already known about this subject

- Nonadherence to antidiabetic medications is common; however, existing methods of detecting nonadherence are time consuming, inefficient, or reliant on integrated pharmacy data not available to all providers.
- Visit-to-visit variability (VTV) in clinical biomarkers has been shown to predict medication adherence in some medical conditions but has not been examined using biomarkers for diabetes such as hemoglobin A1c.

What this study adds

- Using information from a clinical and administrative database, 83% of patients at an urban health center were found to be nonadherent to noninsulin antidiabetic medications, with adherence defined by a medication possession ratio of 80% or greater.
- The proportion of subjects who were nonadherent to antidiabetic medications increased with increasing quintile of VTV of A1c, yet in the adjusted logistic regression model, there was no significant association between VTV of A1c and medication nonadherence.
- When added to other clinical variables, VTV of hemoglobin A1c is not a robust predictor of nonadherence to antidiabetic medications.

Nonadherence to diabetic medications is a prevalent and costly problem. Patients take only an estimated 65%–85% of prescribed doses of oral hypoglycemic agents.^{1,2} Lower rates of adherence are observed in racial minorities,³ Medicaid enrollees,¹ and younger patients.^{4–6} Nonadherence to diabetic medications, antihypertensives, and cholesterol-lowering medications is associated with an increased risk of hospitalization and all-cause mortality,⁷ while satisfactory adherence is associated with decreased likelihood of microvascular complications.⁸ For every 10% increase in adherence to antidiabetic medications, total annual health care costs are projected to decrease by approximately 8.6%.^{9,10}

In order to achieve the benefits of adequate glycemic control, providers and health systems must be able to accurately detect nonadherence. Yet clinicians are insensitive appraisers of adherence, usually overestimating current and future adherence.¹¹ Existing methods of assessing adherence, such as pill counts or validated questionnaires, are vulnerable to social desirability influences and consume time to complete.^{12,13} Unless they are working within an integrated pharmacy system, such as the Veterans Health Administration or health maintenance organizations, providers rarely have access to pharmacy refill information. Sophisticated techniques such as medication event monitoring systems (MEMS) are not widely available outside research studies and require integration of electronic information into the patient record during the relevant clinical visit. Thus, there is a need for efficient, reliable methods to diagnose nonadherence at the point of care.¹⁴

One candidate indicator of low medication adherence is variability in clinical biomarkers that are directly affected by medications. For example, a patient with hypertension

FIGURE 1 Study Flow Diagram

A1c = hemoglobin A1c; BMC = Boston Medical Center.

who is regularly taking antihypertensive medications would be expected to have relatively consistent blood pressure measurements over time. In contrast, inconsistent intake of antihypertensives would be associated with variable blood pressure recordings. In practice, such erratic readings often alert clinicians to possible poor adherence. Rather than rely on clinical intuition alone, this visit-to-visit variability (VTV) in the clinical biomarker could be quantified using electronic health record algorithms and used objectively as a predictor of medication nonadherence during the clinical visit.

Using pharmacy claims data, our group has previously demonstrated that VTV of low-density lipoprotein cholesterol (LDL-C) is associated with nonadherence to statin medications.¹⁵ A similar analysis among patients with hypertension also showed a relationship between increasing VTV of systolic blood pressure and degree of antihypertensive medication nonadherence; however, medication adherence explained only a small fraction of VTV of blood pressure.¹⁶ There remains uncertainty about the ability of VTV of other biomarkers to predict nonadherence to medications.

Given the strong effect that antidiabetic medications have on glycosylated hemoglobin (A1c), we hypothesized that VTV of A1c would be a reliable predictor of nonadherence to antidiabetic medications. VTV of A1c could then be used in the clinical setting to identify patients with low adherence for targeted interventions to improve medication compliance.

Methods

Data Source

Our study sample consisted of patients enrolled in the Boston Medical Center (BMC) Health Plan who received care at BMC or 1 of 8 affiliated community health centers (CHCs) from 2008 to 2012. BMC is the largest safety-net hospital in New England, and the BMC Health Plan is a managed care organization that offers mostly Medicaid and free or heavily subsidized care.

BMC and its affiliated CHCs participate in the Massachusetts Healthcare Disparities Repository (MHDR), a collaborative program that promotes investigations in disparities in access to care and health outcomes by using existing clinical data.¹⁷ The MHDR employs the Informatics for Integrating Biology and the Bedside (I2B2) platform to aggregate de-identified clinical data for research purposes. Data available in MHDR and coordinated in I2B2 include visit dates, diagnoses, laboratory results, and medications, which originate from the electronic health record. Claims data from the BMC Health Plan, including filled prescriptions, are also available through I2B2. This study was approved by the Boston University Institutional Review Board.

Inclusion Criteria

Our sample of interest included adults aged 18 years or older who were taking at least 1 medication for diabetes and who had received at least 1 clinical service in 2008-2012 at BMC (Figure 1). All but 1 subject had a diagnosis of diabetes recorded during the study period (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 250.x). Eligible medication classes during this time period were biguanides (metformin); sulfonylureas (glipizide, glimepiride, glyburide); thiazolidinediones (pioglitazone, rosiglitazone); meglitinides (nateglinide, repaglinide); alpha-glucosidase inhibitors (acarbose, miglitol); dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, linagliptin); incretin mimetics (exenatide, liraglutide);

or combination products (e.g., glipizide/metformin). Subjects taking insulin were excluded given the complexity of measuring adherence to insulin using claims data alone and since diabetic patients requiring insulin represent a different clinical population from patients on noninsulin regimens. Subjects were required to have at least 3 prescription fills within a given class of diabetic medications during the study period and at least 3 A1c measurements between the first and last prescription fill dates.

We further required that subjects have at least 1 visit within a primary care specialty (general medicine, internal medicine, family medicine, women's health, or geriatrics) to reflect subjects whose diabetes is partly managed in a primary care setting rather than exclusively by specialists. Pregnant subjects were also excluded (ICD-9-CM codes 630 to 679.99 and 760 to 779.99) given different glycemic goals and permitted therapies during pregnancy.

Independent Variable

The independent variable was the VVV of A1c between the first and last medication fulfillment dates during the 4-year study period. The VVV of A1c was defined as the within-subject standard deviation (SD) of A1c during the study period and was divided into quintiles for the purposes of analysis. A1c measurements that were outside the 0.1 and 99.9 percentiles were top and bottom coded to those values.

Dependent Variable

The dependent variable was adherence to diabetic medication, defined by the medication possession ratio (MPR). The MPR is calculated as the sum of total days' supply of the medication from the first to the last prescription fill, divided by the total number of days in this period.¹⁸ The MPR was calculated separately for each drug class for all diabetic medications prescribed for a subject using prescription medication claims data from I2B2. Then, an average MPR was calculated with equal weighting of each drug class. The average antidiabetic medication MPR was dichotomized as nonadherent and adherent according to the traditional standard of <80% and ≥80%, respectively.¹²

Covariates

Potential covariates were chosen based on previously reported associations with medication adherence^{4-6,9,10,12,15,16,19} and availability in the MHDR I2B2 system: age at first medication fill during the study period; sex; race/ethnicity (White, Black, Hispanic, or other); total number of ambulatory visits during the study period; total number of primary care visits during the study period; rate of primary care visits during the study period (calculated as number of primary care visits per 6 months); within-subject mean A1c during the study period;

number of A1c measurements during the study period; number of days between the first and last diabetic medication prescription fills; medication drug class; number of drug classes; and the diagnoses of hypertension (ICD-9-CM, codes 401.0x to 405.0x), ischemic heart disease (codes 410.0x to 414.9x), cerebrovascular disease (codes 430.0x to 438.9x), and chronic kidney disease (codes 585.0x to 585.9).

Statistical Analyses

Descriptive data are reported as percentages for categorical variables and mean ±SD for continuous variables. Bivariate associations between covariates and quintiles of VVV of A1c, and between covariates and diabetic medication adherence, were tested using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Unadjusted and adjusted multivariate logistic regression models were created to examine the relationship between VVV of A1c and diabetic medication nonadherence. The adjusted model included covariates that were statistically significantly associated with nonadherence based on bivariate associations and variables deemed important to predicting nonadherence according to literature review. Collinearity diagnostics indicated possible collinearity among 3 variables: rate of primary care visits during the study period, number of days between the first and last diabetic medication prescription fills, and number of A1c measurements. Separate adjusted models were thus created using only 2 of these 3 variables. A fully adjusted model including all important covariates (age, sex, race/ethnicity, within-subject mean A1c, number of A1c measurements, number of days between the first and last diabetic medication prescription fills, and rate of primary care visits during the study period) was then created. Parameter estimates were similar across all adjusted models; therefore, the fully adjusted model was accepted as the final model.

Using the average MPR across drug classes, a patient could be considered adherent if highly adherent to 1 drug class and less adherent to another drug class (e.g., MPR 88% for metformin but MPR 74% to sulfonylureas, yielding an average MPR of 82%). A stricter definition of adherence would require that the MPR be ≥80% for all drug classes. A sensitivity analysis of the fully adjusted model using this latter definition of adherence was performed.

The Hosmer-Lemeshow test for goodness-of-fit was used to evaluate the models. For all logistic regression models, the odds ratio (OR) and 95% confidence intervals (CIs) were calculated, and $P < 0.05$ was used for all significance levels. The performance of each model at discriminating diabetic medication adherence from nonadherence was assessed by plotting the receiver operator characteristic (ROC) curve and calculating the C-statistic. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

TABLE 1 Association of VVV of A1c and Sociodemographic and Clinical Variables, 2008-2012

	VVV of A1c (Quintiles) ^a						P Value
	Q1: ≤0.31 N = 127, N (%)	Q2: >0.31-≤0.49 N = 125, N (%)	Q3: >0.49-≤0.75 N = 126, N (%)	Q4: >0.75-≤1.15 N = 128, N (%)	Q5: > 1.15 N = 126, N (%)	Overall N = 632, N (%)	
Sex							
Female	80.0 (63.0)	73.0 (58.4)	65.0 (51.6)	69.0 (53.9)	58.0 (46.0)	345.0 (54.6)	0.0733
Male	47.0 (37.0)	52.0 (41.6)	61.0 (48.4)	59.0 (46.1)	68.0 (54.0)	287.0 (45.4)	
Age at first Rx fill (years)	53.8 (8.3)	52.1 (8.0)	52.8 (7.9)	50.5 (7.7)	49.1 (9.3)	51.7 (8.4)	<0.0001
Race							
White	14.0 (11.3)	18.0 (14.8)	16.0 (12.7)	17.0 (13.4)	16.0 (12.9)	81.0 (13.0)	0.5383
Black	66.0 (53.2)	61.0 (50.0)	60.0 (47.6)	61.0 (48.0)	75.0 (60.5)	323.0 (51.9)	
Hispanic	24.0 (19.4)	16.0 (13.1)	19.0 (15.1)	22.0 (17.3)	16.0 (12.9)	97.0 (15.5)	
Other	20.0 (16.1)	27.0 (22.1)	31.0 (24.6)	27.0 (21.3)	17.0 (13.7)	122.0 (19.6)	
Outpatient visits	37.2 (29.9)	49.4 (40.4)	37.4 (26.5)	45.4 (35.6)	36.6 (25.8)	41.2 (32.5)	0.0143
Primary care visits ^b	12.0 (9.0)	16.0 (14.2)	13.7 (8.6)	16.6 (10.9)	15.0 (8.6)	14.7 (10.6)	0.0003
Rate of primary care visits/6 months	3.0 (3.0)	3.1 (4.9)	2.7 (1.8)	2.6 (1.4)	2.5 (1.5)	2.8 (2.8)	0.8597
Diagnoses							
Diabetes mellitus	126.0 (99.2)	125.0 (100.0)	126.0 (100.0)	128.0 (100.0)	126.0 (100.0)	631.0 (99.8)	0.7975
Hypertension	110.0 (86.6)	111.0 (88.8)	110.0 (87.3)	110.0 (85.9)	106.0 (84.1)	547.0 (86.6)	0.8644
Ischemic heart disease	13.0 (10.2)	14.0 (11.2)	12.0 (9.5)	12.0 (9.4)	16.0 (12.7)	67.0 (10.6)	0.9087
Cerebrovascular disease	6.0 (4.7)	9.0 (7.2)	2.0 (1.6)	7.0 (5.5)	5.0 (4.0)	29.0 (4.6)	0.2996
Chronic kidney disease	13.0 (10.2)	9.0 (7.2)	10.0 (7.9)	12.0 (9.4)	10.0 (7.9)	54.0 (8.5)	0.9118
A1c measurements	4.9 (2.5)	6.7 (3.3)	6.1 (3.4)	7.2 (3.7)	6.6 (2.9)	6.3 (3.3)	<0.0001
Within-subject mean A1c	6.7 (0.9)	6.9 (0.8)	7.7 (0.9)	8.1 (1.2)	8.9 (1.2)	7.7 (1.3)	<0.0001
Days between first and last fill dates	850.2 (465.3)	1,107.0 (496.9)	1,040.5 (506.1)	1,155.4 (494.4)	1,181.3 (492.0)	1,066.8 (503.7)	<0.0001
Number of drug classes							
1	88.0 (69.3)	64.0 (51.2)	36.0 (28.6)	40.0 (31.3)	38.0 (30.2)	266.0 (42.1)	<0.0001
2	29.0 (22.8)	47.0 (37.6)	65.0 (51.6)	54.0 (42.2)	66.0 (52.4)	261.0 (41.3)	
3	10.0 (7.9)	14.0 (11.2)	23.0 (18.3)	32.0 (25.0)	22.0 (17.5)	101.0 (16.0)	
4	0	0	2.0 (1.6)	2.0 (1.6)	0	4.0 (0.6)	
Antidiabetic MPR ^c							
<80%	101.0 (79.5)	96.0 (76.8)	101.0 (80.2)	110.0 (85.9)	118.0 (93.7)	526.0 (83.2)	0.0027
≥80%	26.0 (20.5)	29.0 (23.2)	25.0 (19.8)	18.0 (14.1)	8.0 (6.4)	106.0 (16.8)	

Note: Data are presented as mean ± SD or n (%).

^aVVV of A1c was defined by within-subject standard deviation of A1c.

^bPrimary care visits were defined as visits to Family Medicine, General Medicine, Women's Health, Primary Care, and Geriatrics.

^cMPR was averaged across medication classes for subjects taking medications from more than 1 drug class. Nonadherence was defined as MPR < 80%.

A1c = hemoglobin A1c; MPR = medication possession ratio; Q = quintiles; Rx = prescription; SD = standard deviation; VVV = visit-to-visit variability.

Results

A total of 632 adults with at least 3 noninsulin diabetic medication fills and at least 3 A1c measurements between the first and last medication fills were identified between 2008 and 2012 (Figure 1). The majority of subjects were female (54.6%) and Black (51.9%), and the mean age in the sample was 52 years (Table 1). Subjects contributed an average of almost 3 years of pharmacy prescription information (mean 1,067 days [SD 504] between first and last prescription fills). Almost 58% of the sample was taking more than 1 drug for diabetes, most commonly metformin (89.9%) and sulfonylureas (57.9%; data not shown). The average within-subject mean A1c level was 7.7% ± 1.3%.

Table 1 shows the association between VVV of A1c and sociodemographic and clinical covariates. As the VVV of A1c

increased, mean age decreased significantly. The number of A1c measurements, the within-subject mean A1c, and the number of days between the first and last medication fills increased significantly with increasing quintile of VVV of A1c. There was no significant association between VVV of A1c and race, sex, or proportion with comorbidities of interest.

Approximately 83% of the sample met criteria for nonadherence, and nonadherence was significantly associated with younger age and Black race (Table 2). A greater number of A1c measurements, higher within-subject mean A1c, and a longer interval between first and last fill dates were significantly associated with medication nonadherence. Subjects with hypertension were more likely to be adherent than those without hypertension; no significant associations were found for other diagnoses.

TABLE 2 Association of Medication Adherence and Sociodemographic and Clinical Variables, 2008-2012

	Antidiabetic MPR ^a						<i>P</i> Value
	MPR <80% N = 526, N (%)		MPR ≥80% N = 106, N (%)		Overall N = 632, N (%)		
Sex							
Female	287.0	(54.6)	58.0	(54.7)	345.0	(54.6)	0.9768
Male	239.0	(45.4)	48.0	(45.3)	287.0	(45.4)	
Age at first Rx fill (years)	51.0	(8.5)	55.2	(6.5)	51.7	(8.4)	<0.0001
Race							
White	63.0	(12.1)	18.0	(17.3)	81.0	(13.0)	0.0099
Black	284.0	(54.7)	39.0	(37.5)	323.0	(51.9)	
Hispanic	79.0	(15.2)	18.0	(17.3)	97.0	(15.5)	
Other	93.0	(17.9)	29.0	(27.9)	122.0	(19.6)	
Outpatient visits	42.0	(32.2)	37.5	(33.8)	41.2	(32.5)	0.0490
Primary care visits ^b	15.1	(9.7)	12.6	(14.1)	14.7	(10.6)	<0.0001
Rate of primary care visits/6 months	2.7	(1.9)	3.2	(5.5)	2.8	(2.8)	0.7451
Diagnoses							
Diabetes mellitus	525.0	(99.8)	106.0	(100.0)	631.0	(99.8)	1.0000
Hypertension	448.0	(85.2)	99.0	(93.4)	547.0	(86.6)	0.0277
Ischemic heart disease	53.0	(10.1)	14.0	(13.2)	67.0	(10.6)	0.3860
Cerebrovascular disease	24.0	(4.6)	5.0	(4.7)	29.0	(4.6)	1.0000
Chronic kidney disease	43.0	(8.2)	11.0	(10.4)	54.0	(8.5)	0.4593
Number of A1c measurements	6.4	(3.2)	5.8	(3.3)	6.3	(3.3)	0.0116
Within-subject mean A1c	7.8	(1.3)	7.2	(0.9)	7.7	(1.3)	0.0003
Days between first and last fill dates	1,109.4	(496.8)	855.1	(486.3)	1,066.8	(503.7)	<0.0001
Number of drug classes							
1	216.0	(41.1)	50.0	(47.2)	266.0	(42.1)	0.5150
2	219.0	(41.6)	42.0	(39.6)	261.0	(41.3)	
3	87.0	(16.5)	14.0	(13.2)	101.0	(16.0)	
4	4.0	(0.8)	0		4.0	(0.6)	

Note: Data are presented as mean ± SD or n (%).

^aMPR was averaged across medication classes for subjects taking medications from more than 1 drug class. Nonadherence was defined as MPR <80%.

^bPrimary care visits were defined as visits to Family Medicine, General Medicine, Women's Health, Primary Care, and Geriatrics.

A1c = hemoglobin A1c; MPR = medication possession ratio; Rx = prescription; SD = standard deviation.

The proportion of subjects who were nonadherent increased overall with increasing quintiles of VVV of A1c (79.5%, 76.8%, 80.2%, 85.9%, 93.7%, $P=0.0027$ for association; Table 1). In the unadjusted logistic regression model, there was a moderately strong association between VVV of A1c and nonadherence to diabetic medication that was statistically significant for the highest quintile (OR=3.80, 95% CI=1.65-8.76; Table 3). However, the fully adjusted model showed no association between VVV of A1c and nonadherence. In a sensitivity analysis using the stricter definition of adherence (i.e., MPR ≥80% for all drug classes), there remained no significant association.

ROC curves for the models demonstrate that addition of VVV of A1c does not add substantially to the discrimination between adherence and nonadherence to diabetic medications (Figure 2). The C-statistic for the model when only age, sex, and race are included is 0.6786; adding VVV of A1c modestly improves the C-statistic to 0.7064. Similarly, adding VVV of A1c to a model that includes age, sex, race, within-

subject mean A1c, number of A1c measurements, number of days between first and last prescription fill dates, and rate of primary care visits improves the C-statistic marginally from 0.7460 to 0.7525.

Discussion

Unlike previous studies examining the ability of VVV to predict medication nonadherence,^{15,16} we did not find that VVV of A1c was a significant predictor of nonadherence to noninsulin diabetic medications when added to other clinical information. However, consistent with prior research,^{20,21} younger age, Black race, and higher mean A1c levels were statistically significantly associated with medication nonadherence.

Given that nearly 60% of subjects were on more than 1 antidiabetic agent, polypharmacy may have complicated the relationship between medication adherence and VVV of A1c. Full therapeutic doses of metformin and thiazolidinediones can lower A1c by 1%-2% and 0.5%-1.4%, respectively.²² In

TABLE 3 Logistic Regression Models Predicting Odds of Antidiabetic Nonadherence According to Quintile of VVV of A1c, 2008-2012

	Unadjusted Model ^a		Final Adjusted Model ^b			
	OR (95% CI)		P Value		OR (95% CI)	P Value
VVV of A1c ^c						
1st quintile (reference)	1.00	(-)	0.0052	1.00	(-)	0.4070
2nd quintile	0.85	(0.47-1.55)		0.62	(0.32-1.21)	
3rd quintile	1.04	(0.56-1.92)		0.65	(0.32-1.33)	
4th quintile	1.57	(0.81-3.04)		0.69	(0.31-1.57)	
5th quintile	3.80	(1.65-8.76)		1.19	(0.42-3.38)	
Sex						
Female (reference)				1.00	(-)	0.9133
Male				1.03	(0.65-1.63)	
Age at first antidiabetic Rx fill						
1-year increase				0.94	(0.91-0.97)	0.0004
Race						
White				0.49	(0.25-0.95)	0.0371
Black (reference)				1.00	(-)	
Hispanic				0.59	(0.31-1.14)	
Other				0.47	(0.26-0.84)	
Rate of primary care visits/6 months ^d				1.01	(0.95-1.08)	0.6937
Days between first and last fill dates				1.00	(1.00-1.00)	<0.0001
Number of A1c measurements				0.87	(0.78-0.98)	0.0181
Within-subject mean A1c				1.42	(1.06-1.89)	0.0181

Note: Nonadherence was defined as MPR < 80% averaged across antidiabetic medication classes.

^aHosmer-Lemeshow goodness-of-fit test, $P = 1.000$.

^bHosmer-Lemeshow goodness-of-fit test, $P = 0.1734$.

^cVVV of A1c was defined as within-subject standard deviation of A1c during the study period.

^dPrimary care visits were defined as visits to Family Medicine, General Medicine, Women's Health, Primary Care, and Geriatrics.

A1c = hemoglobin A1c; CI = confidence interval; MPR = medication possession ratio; OR = odds ratio; Rx = prescription; VVV = visit-to-visit variability.

comparison, the starting dose of simvastatin lowers LDL-C by 30%.²³ The stronger relationship between VVV of LDL-C and statin nonadherence¹⁵ may be due to use of a single agent to affect LDL-C and the powerful impact that statins have on cholesterol metabolism. The degree to which a medication can change a biomarker may affect the degree to which variability in the biomarker might be explained by medication adherence.

By reducing absolute A1c and fluctuations in glucose levels, improvements in diet, exercise, and weight may be expected to reduce A1c variability as well.²⁴ Unfortunately, in this study, weight data were available within 30 days of the first and last prescription fills for less than one-third of subjects. In the case of LDL-C, statin medications are even more potent than diet and exercise in altering cholesterol levels; therefore, adherence to statins may account for more variability in LDL than adherence to diabetic medications accounts for variability in A1c.

Finally, the natural history of diabetes is one of progressive insulin resistance and loss of endogenous insulin production leading to worsening glycemic control. Increase in A1c, and perhaps A1c variability as well, may be expected even with

ideal medication adherence, although the rapidity may be altered by medication compliance and intensification.^{24,25}

Many studies have shown lower rates of adherence among Black patients with diabetes,^{5,6,19} although this association is not consistent across diseases.¹² Over half of our sample was Black, and while race was not associated with quintile of VVV of A1c, it was significantly associated with nonadherence. A1c levels are higher in Black individuals compared with White individuals across the glycemic spectrum,²⁶ even when controlling for other predictors of A1c, and this discrepancy is most pronounced among diabetics.²⁷ These racial differences should not affect VVV, which is a measure of within-subject variability, but it may explain differences in mean A1c by race in our sample. Our findings of lower adherence among younger subjects is consistent with other studies of medication adherence among diabetic patients, both young adults and seniors.⁴⁻⁶ This association may be related to duration of disease, severity of illness, or management of multiple chronic diseases. These demographic findings support interventions to improve adherence to diabetic medications among young patients and those from minority communities.

FIGURE 2 ROC Curves for Identification of Antidiabetic Medication Nonadherence

Legend	ROC Model	C-statistic (Area Under Curve)
—	Age, sex, race	0.6786
—	Age, sex, race, VVV of A1c	0.7064
—	Age, sex, race, within-subject mean A1c, number of A1c measurements, number of days between first and last prescription fill dates, rate of primary care visits	0.7460
—	Age, sex, race, within-subject mean A1c, number of A1c measurements, number of days between first and last prescription fill dates, rate of primary care visits, VVV of A1c	0.7525

Note: Sequential ROC curves for identification of antidiabetic nonadherence (defined as antidiabetic MPR <80%) using sociodemographic and clinical variables. Addition of VVV of A1c to the final model improves the C-statistic from 0.7460 to 0.7525 (95% CI=0.7021-0.8029).

A1c=hemoglobin A1c; CI=confidence interval; MPR=medication possession ratio; ROC=receiver operator characteristic; VVV=visit-to-visit variability.

While we are the first to explore an association between VVV of A1c and medication adherence, increased variability in A1c is already recognized as a marker of elevated risk for diabetic complications. In the Finnish Diabetes Nephropathy longitudinal cohort study of patients with type 1 diabetes, investigators found that variability in A1c predicted development and progression of renal disease as well as cardiovascular events such as myocardial infarction and stroke.²⁸ Similarly, among subjects with type 2 diabetes, researchers have found that variability in A1c predicted microalbuminuria and progression of nephropathy, independent of mean A1c.^{29,30} In a study using a clinical database, type 2 diabetics with high

variability in A1c had nearly twice the risk of all-cause mortality compared with subjects with low variability.³¹ These findings parallel studies of variability in systolic blood pressure, which has been associated with increased risk for stroke and all-cause mortality, independent of mean blood pressure.^{32,33} More research is needed on the biological basis for this variability in clinical biomarkers and the extent to which specific medication classes and medication adherence may account for this variability.

Limitations

Our sample consists of insured but low-income patients who are largely of minority race/ethnicity at a single urban health care system; thus, the findings may not apply to other settings. Still, the challenge of medication nonadherence may be greatest in such a population and merits particular attention. Indeed, the MHDR database used in this study was intended to promote research in health care disparities according to race and socioeconomic status. As a younger, non-Medicare sample, this population is also where early, aggressive management of diabetes is essential.

Adherence to oral diabetic medications in most studies has ranged from 65%-85% yet is often lower (36%-53%) in populations that are similar to ours.¹ The average MPR in our sample was 56.2%, and the rate of medication nonadherence was 83.2%, again limiting generalizability but arguing for the disproportionate burden of the problem of adherence in this community.

Over half of our subjects had nearly 3 years of pharmacy prescription information, but we did not assess for change in adherence over that time period, which may occur as patients live with and adapt to their medical conditions. All subjects included in the sample had at least 1 visit with a primary care specialty, which enhances the utility of these results to primary care practitioners, although prescriptions and some management may have been shared with specialists. Although the I2B2 system is a rich collection of important variables, some covariates, such as duration of diabetes, are not available. Future research should consider longitudinal studies to assess temporal trends in adherence and A1c variability.

We used pharmacy claims to measure medication adherence, which may overestimate adherence, since it cannot account for pill storing or pill dumping of acquired medications but has been shown to be a reliable and practical method for health services research.³⁴ Future studies should consider replicating analyses using a more rigorous measure of adherence, such as pill counting or MEMS, to test the validity of these findings. We excluded subjects using insulin due to the complexities of measuring dose and compliance, the markedly increased A1c variability that insulin induces, and to achieve a more clinically homogenous sample of diabetic patients. If adherence to insulin could be efficiently measured, it would be important to test the utility of VVV of A1c in predicting adherence in that patient population. We did include subjects

on relatively newer diabetic medications, such as incretin mimetics and DPP-4 inhibitors, while most previous studies on medication adherence among diabetics have been restricted to biguanides, sulfonylureas, or other oral agents. We could not account for medications that patients may have obtained without submitting pharmacy prescription claims data, such as free antidiabetic medications available at some large retailers. There is a risk of misclassification bias if patients were not continuously enrolled in the health plan during the study period. If patients temporarily disenrolled and received prescriptions through another plan and then re-enrolled in BMC Health Plan, their MPR would appear falsely low and may have biased our results.

Additional factors associated with poor medication adherence, including polypharmacy,¹² dose frequency,³⁵ burden of comorbid diseases,²¹ cost of copayments for medications,³⁶ and psychosocial factors such as personal health beliefs,³⁷ health literacy,³⁸ and depression,³⁹ were not measured in this study. We did include specific diagnoses that often co-occur with diabetes, such as hypertension, or that might affect diabetic medication prescribing practices, such as chronic kidney disease. With the exception of hypertension, these diseases were not associated with nonadherence.

Conclusions

We found that VVV of A1c is not a robust indicator of nonadherence to noninsulin diabetic medications. Efficient, reliable means of detecting nonadherence at the bedside are still needed in order to diagnose at-risk patients and deliver intervention to appropriate patients. Researchers and health care systems should explore innovative approaches that leverage health information technology to measure adherence, such as integrating patient information (e.g., MEMS data) or pharmacy information directly into electronic health records to create useful alerts for physicians at the point of care.

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Study concept and design were contributed by Mann, Winter, and Ramachandran. Winter collected data, assisted by Mann, and all authors contributed equally to data analysis. The writing and revision of the manuscript were carried out primarily by Ramachandran, assisted by Winter and Mann.

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