



Factors Associated with Secondary Nonadherence to Oral Anti-hyperglycemic Agents Among Patients with T2DM

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Abstract

Glycemic control in patients with T2DM remains sub-optimal. A major contributor to poor goal achievement is medication nonadherence. This study aimed to examine secondary nonadherence to oral anti-hyperglycemic agents (AHA) among T2DM patients and to assess its association with community- and individual-level characteristics.

Using claims and electronic medical records in Geisinger Health System from 2003 to 2015, this retrospective cohort study included adults with newly diagnosed T2DM who filled their first order of oral AHA. Secondary nonadherence was determined when patients did not fill the second oral AHA prescription within 30 days after the first fill supply ended.

Among 2,413 patients who filled the first order, 764 (31.7%) were not adherent to the second prescription. Younger age, non-white (vs. white) and chronic kidney disease were associated with higher odds of nonadherence. Patients with higher baseline HbA1c when $\leq 10\%$ were associated with lower odds of nonadherence, while those with higher baseline HbA1c when $>10\%$ were more likely to be non-adherent. Community-level characteristics were not found to be associated with nonadherence. Nearly one-third of patients did not complete a second fill of their oral AHA.

This study identified patient characteristics associated with secondary nonadherence that may provide intervention points for improving medication adherence in diabetes management.

Background

According to the National Diabetes Statistics Report 2017 (1):

- More than 30 million (12.2%) US adults had diabetes in 2015. Diabetes prevalence increased with age — 25.2% of those 65 years old or older had diabetes.
- Asian, non-Hispanic blacks, and Hispanics had higher prevalence of diabetes compared to non-Hispanic whites. American Indians/Alaska Natives had the highest prevalence of diagnosed diabetes.
- Socioeconomic status was associated with prevalence of diabetes:
 - 12.6% of adults with less than high school education were diagnosed with diabetes,
 - 9.5% of those with high school diplomas,
 - 7.2% of those with more than a high school education.
- In an examination of county-level prevalence of diagnosed diabetes, prevalence ranged from 3.8% to 20%

ADA Recommendations

The American Diabetes Association (ADA) recommends oral therapy, including metformin, in addition to lifestyle management for patients with mild to moderately uncontrolled type 2 diabetes (2). Oral therapy with one or more agents can reduce HbA1c values by over 2%; however, the proportion of patients reaching targeted HbA1c control (i.e., $< 7\%$) remains below 50%.

A major contributor to this poor goal achievement is medication nonadherence (3-5). Rates of adherence to oral antidiabetic medications are reported to range from 65% to 85% for patients on treatment 6-24 months (6).

Review of Literature on Nonadherence

- One study found that approximately 15% of patients prescribed new oral antidiabetic agents never fill their first prescription. And those with higher HbA1c ($>9\%$) and lower copayments ($< \$10$) were more likely to fill their first prescription (7).
- In a recent randomized controlled study, researchers found that despite outreach by nurses to those not filling after 14 days, rates of first fill are only marginally improved, and are no different from no intervention (8).
- Individuals characterized as loyal to a specific pharmacy were more likely to be adherent to their diabetes medications when compared to 'non-loyal' patients (9).

This Research

We examined individual and community-level characteristics, using data extracted from electronic health records in Geisinger Health to identify traits associated with secondary nonadherence (no second refill) to oral anti-hyperglycemics. Specifically we were interested in:

- demographics;
- health status, including comorbid and co-occurring conditions;
- health care utilization; and
- social determinants at the community level.

Data and Methods

- Retrospective cohort study during years of 1/1/2005 – 9/30/2015. Patients included in the study were:
 - adult patients 18 years or older with type 2 diabetes.
 - oral antidiabetic medication prescribed after meeting the definition of type 2 diabetes and restricted to have continuous Geisinger Health Plan Rx coverage 30 days after the prescription.
- Type 2 diabetes defined as meeting 1 of 3 conditions:
 - HgbA1c > 7.0 ; or,
 - 3 fasting blood glucose measures > 15 ; or,
 - type 2 diabetes ICD-9-CM code (ICD-9 250.xx)
 The criteria also included no signal for type 2 diabetes for at least 2 years in the EMR prior to the diagnosis to ensure the patient did not enter the health system with the condition.
- Social characteristics collected included age, sex, race/ethnicity, marital status and place of residence.
- Clinical characteristics included comorbidity burden, most current HgbA1c and glucose values, and health care utilization in the prior 12 months of the medication order.
- Addresses of individuals in the study were geocoded and linked to census data in order to create proxy measures for socioeconomic status based on neighborhood level indicators.
- Antidiabetic medication orders were linked to the Geisinger Health Plan to search for fills.

Statistical Analysis

Secondary non-adherence was defined as filling the second prescription within 30 days following the initial fill (7). Baseline variables are described using mean and standard deviations for those measured continuously, and frequency and percentage for those collected as categorical. Comparisons between groups was accomplished using the 2-sample t-test, Wilcoxon Rank sum, and Pearson's Chi-Square tests, as appropriate.

A logistic regression model was then fit that included all variables found to be different between adherent and non-adherent at a p-value < 0.20 . Variables were removed from the model if they were not significant at $p < 0.20$. Results are presented as odds ratios and corresponding 95% CIs. Baseline HgbA1c exhibited a non-linear relationship with secondary nonadherence and thus were analyzed using piecewise linear spline with a knot at 10%, modeling different slopes for HgbA1c $>$ or \leq to 10.

Bivariate Results	Secondary Non-Adherence N (%) / Mean (SD) N=764	Secondary Adherent N (%) / Mean (SD) N=1649	P-Value
Age	57.0 (47.0, 67.0)	58.0 (49.0, 69.0)	0.1433
Male Sex	378 (49.5%)	835 (50.6%)	0.5959
White Race	732 (95.8%)	1614 (97.9%)	0.0041
Current Smoker	103 (13.5%)	268 (16.2%)	0.0792
Marital Status			0.0254
Divorced/Separated	73 (9.6%)	213 (12.9%)	
Married	483 (63.2%)	1020 (61.9%)	
Single	119 (15.6%)	206 (12.5%)	
Widowed	89 (11.6%)	210 (12.7%)	
Utilization in Past 12 Months			
Primary Care Visits	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	0.5039
Emergency Department Only			0.1017
0	653 (85.5%)	1449 (87.9%)	
1+	111 (14.5%)	200 (12.1%)	
Hospitalizations			
0	678 (88.7%)	1490 (90.4%)	0.2220
1+	86 (11.3%)	159 (9.6%)	
Number of Active Medications			0.2363
0	402 (52.6%)	911 (55.2%)	
1-5	126 (16.5%)	284 (17.2%)	
6+	236 (30.9%)	454 (27.5%)	
First Medication Ordered: Metformin	568 (74.4%)	1285 (77.9%)	0.0526
0	402 (52.6%)	911 (55.2%)	
1-5	126 (16.5%)	284 (17.2%)	
6+	236 (30.9%)	454 (27.5%)	
First Medication Ordered: Metformin	568 (74.4%)	1285 (77.9%)	0.0526
Charlson Comorbidity Index	2.0 (1.0, 4.0)	3.0 (1.0, 4.0)	0.8845
CKD	21 (2.8%)	21 (1.3%)	0.0100
HbA1c	7.3 (6.9, 8.4)	7.5 (7.0, 8.8)	0.0044
Glucose	157.0 (134.0, 192.)	160.0 (135.0, 210.0)	0.0853
Census Characteristics – Block Group			
Median Household Income	\$47031 (\$38021, \$56667)	\$47721 (\$38333, \$56458)	0.9759
% Poverty	7.53% (4.74%, 10.67%)	7.30% (4.74%, 10.35%)	0.3890
% 65+	17.01% (14.67%, 19.97%)	16.88% (14.73%, 19.51%)	0.2858
Race/Ethnicity			
% Owner Occupied Housing Units	80.39% (62.61%, 87.29%)	80.38% (63.69%, 87.18%)	0.9585
% Bachelor's Degree or Higher	17.80% (11.36%, 25.84%)	16.78% (10.93%, 24.65%)	0.3548
Race			
%White	97.2% (94.2%, 98.3%)	97.1% (94.5%, 98.3%)	0.5973
%Black	0.7% (0.3%, 1.6%)	0.7% (0.3%, 1.6%)	0.6398
%Other	2.2% (1.4%, 4.1%)	2.2% (1.3%, 3.7%)	0.3278
Ethnicity			
%Hispanic	1.4% (0.8%, 3.2%)	1.4% (0.8%, 2.9%)	0.8484
%Non-Hispanic	98.6% (96.8%, 99.2%)	98.6% (97.1%, 99.2%)	0.8651

Logistic Regression of Secondary Nonadherence to Oral Anti-Hyperglycemic Agents

Variable	Odds Ratio (95% CI)	P-Value
Age	0.99 (0.98, 0.998)	0.0152
White Race	0.50 (0.30, 0.84)	0.0091
Current Smoker	0.78 (0.59, 1.01)	0.0628
≥ 1 ED Visit in Prior 12 Months	1.27 (0.98, 1.66)	0.0718
1 st Medication Order: Metformin	0.83 (0.67, 1.03)	0.0935
Chronic Kidney Disease	1.97 (1.03, 3.76)	0.0411
HbA1c		0.0004
$\leq 10\%$	0.83 (0.76, 0.91)	
$> 10\%$	1.14 (1.01, 1.30)	

ED = Emergency Department

All variables significant at the $p < 0.20$ level in bivariate analysis were considered in the logistic regression model. Baseline HbA1c exhibited a non-linear relationship with secondary nonadherence. Piecewise linear splines with a knot at 10% was used in this model to allow for a different slope of HbA1c $\leq 10\%$ and $> 10\%$

The bivariate analysis revealed significant associations with secondary nonadherence including:

- current smoker status \uparrow
- marital status — single \uparrow
- first medication ordered was metformin \uparrow
- chronic kidney disease \uparrow
- HgbA1c associated with nonadherence
- community social determinants were not associated with differences in adherence.

Multivariate analysis revealed the following significant predictors of nonadherence:

- younger age
- non-white race
- chronic kidney disease
- HgbA1c > 10

Conclusion

- There are differences in likelihood of filling diabetes medication like metformin a second time by demographic and clinical characteristics.
- Secondary adherence is perhaps a more important indicator of long-term adaptation to diabetes management and requires thoughtful intervention in observed nonadherence.
- Interventions to promote adherence to diabetes management may require differentiated approaches for patients in subgroups. It is important to understand the values and resources of patients in order to develop diabetes management strategies that are appealing and deemed important by patients.
- Further research is necessary to characterize those values and resources in order to improve the development of patient-engaged diabetes-management strategies.

Limitations

- Prescription refill information is available only on patients who have Geisinger health care coverage. It is unclear if the same characteristics would emerge for patients with different coverage or for those who had no coverage during some portion of the study period.
- The study period covers both pre- and post -ACA. It may be important to better understand the implications of this timing, since there was a significant increase in the proportion of the population covered, and those with newly acquired insurance may have been more likely to begin filling prescriptions.
- Some of the patients identified as non-adherent for the second fill may have had a clinical indication that caused their provider to change the medication, e.g., chronic kidney disease.
- There is no patient-reported data regarding barriers to taking medication.

References

- Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017.
- Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32(1):133-203.
- Krappek K, King K, Warren SS, et al. Medication adherence and associated hemoglobin A1c in type 2 diabetes. *Ann Pharmacother*. 2004;38(9):1357-1362.
- Schechtman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. *Diabetes Care*. 2002;25(6):1015-1021.
- Dunbar-Jacob J, Mortimer-Stephens M. Treatment adherence in chronic disease. *J Clin Epidemiol*. 2001;54(12):S60.
- Rubin RR. Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus. *Am J Med*. 2005;118(5):27-34.
- Shah NR, Hirsch AG, Zacker C, Taylor S, Wood GC, Stewart WF. Factors associated with first-fill adherence rates for diabetic medications: A cohort study. *Journal of general internal medicine*. 2009;24(2):233-237.
- Fischer MA, Jones JB, Wright E, et al. A randomized telephone intervention trial to reduce primary medication nonadherence. *Journal of managed care & specialty pharmacy*. 2015;21(2):124-131.
- Dossa AR, Gregoire JP, Lauzier S, Guenette L, Stross C, Moisan J. Association between loyalty to community pharmacy and medication persistence and compliance, and the use of guidelines-recommended drugs in type 2 diabetes: A cohort study. *Medicine (Baltimore)*. 2015;94(27):e1082.