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Nonadherence to Oral Antihyperglycemic Agents: Subsequent Hospitalization and Mortality among Patients with Type 2 Diabetes in Clinical Practice

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Abstract

Using real-world clinical data from the Indiana Network for Patient Care, we analyzed the associations between non-adherence to oral antihyperglycemic agents (OHA) and subsequent diabetes-related hospitalization and all-cause mortality for patients with type 2 diabetes. OHA adherence was measured by the annual proportion of days covered (PDC) for 2008 and 2009. Among 24,067 eligible patients, 35,507 annual PDCs were formed. Over 90% (n=21,798) of the patients had a PDC less than 80%. In generalized linear mixed model analyses, OHA non-adherence is significantly associated with diabetes related hospitalizations (OR: 1.2; 95% CI [1.1,1.3]; p<0.0001). Older patients, white patients, or patients who had ischemic heart disease, stroke, or renal disease had higher odds of hospitalization. Similarly, OHA non-adherence increased subsequent mortality (OR: 1.3; 95% CI [1.02, 1.61]; p<0.0001). Patient age, male gender, income and presence of ischemic heart diseases, stroke, and renal disease were also significantly associated with subsequent all-cause death.

Keywords

Health information exchange, type 2 diabetes, medication adherence, hospitalization, mortality

Background

Type 2 diabetes is a major public health crisis in this country. Over 29 million adults in the United States currently have diabetes mellitus, and the incidence is increasing at nearly epidemic rates [1]. This will have a significant public health impact because diabetes is a major cause of morbidity and mortality. In addition, healthcare costs are 11% higher for patients with poorly controlled diabetes compared to those with good glycemic control [2].

Clearly, pharmacotherapy for glycemic control is essential to achieving the goal of long-term metabolic control and reducing the risk of cardiovascular disease (CVD) events, the primary cause of hospitalization and mortality among these patients. However, increasing evidence suggests that patients with diabetes often have poor adherence to prescribed medication therapies. A systematic review of medication adherence in diabetes showed low adherence rates, ranging between 36-87% across numerous studies [3]. These observations have been replicated in several studies, and adherence among patients with diabetes is disappointingly low, dropping most dramatically after the first six months of therapy [4,5].

Improving medication adherence is viewed as a high priority for health care reform. The Centers for Medicare and Medicaid Service (CMS) has encouraged adherence to oral diabetes medications via quality and efficiency measures in health and drug plan performance rating [6]. However, improving medication adherence is a multifactorial challenge. Health information technology (HIT) and health information exchange (HIE) are playing an increasing role in generating, measuring, and transferring important medication adherence data between hospitals, pharmacies, providers, and patients. Recently, the electronic medical record system (EMR) meaningful use criteria and the Accountable Care Organization (ACO) have encouraged electronic prescribing, medication reconciliation, patients' accessibility to their own medical information, and care coordination [7,8], all of which support improving medication adherence and ultimately improving patient health outcomes through HIT and HIE.

Although the effects of medication adherence on patient hospitalization and mortality, as well as the significant potential of HIT and HIE for improving medication adherence, have been increasingly recognized, few population-based studies have been conducted using real-world data. The association between medication non-adherence and mortality has been chiefly demonstrated in clinical trials. In this study, we aimed to assess adherence to OHA for patients with type 2 diabetes and to analyze the association between OHA non-adherence and hospitalization and mortality, using real-world clinical data from an operational HIE.

Methods

Data sources and settings

This retrospective study was designed to analyze the association between nonadherence to oral antihyerglycemic agents (OHA) and health outcomes in the subsequent year for patients with type 2 diabetes. We used medication dispensing data from 2008 to 2009 and clinical data (hospitalization and death) from 2009 to 2010 from the Indiana Network for Patient Care (INPC). The INPC is an operational, regional, health information exchange that included over 100 hospitals, physician practices, payers, pharmacies, laboratories, and independent radiology centers. This system delivers medical record information from hospitals, laboratories, imaging centers, pharmacies and physician offices [9]. In particular the INPC included pharmacy claims data from the largest public and private payers as well as medication history data from pharmacy benefit managers obtained via the Surescripts network [10]. For this study, the patient medication history, diabetes related hospitalizations, and death (all causes) information were extracted from the INPC and were linked through a robust linkage algorithm. We additionally estimated patient income through median household income by zip code obtained from the U.S. Census Bureau website (2000 data is the most recently information available). This

study was approved by the Institutional Review Board of Indiana University and the INPC Management Committee.

Eligibility criteria

Eligible subjects were age 18 years or older in 2008, and had a diagnosis of type 2 diabetes using the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9_CM) of 250.x0 and 250.x2. They had at least one pharmacy claim for an OHA: Biguanides, Sulfonylurea (SU), Thiazolidinedione (TZD), other OHAs (Meglitinides and α- glucosidase), or OHA combination. Patient OHA dispensing information was extracted by the National Drug Codes (NDC) with drug names matched to OHA medications identified by the First DataBank *Standard Therapeutic Code* system (STC:71, excluding injectable: 0177, A771, A716), from 2008 to 2009. Patients who used insulin were excluded. This sample reflects patients who had a drug benefit. Also, since all included subjects had in fact filled a prescription, it suggests that they used that benefit. Therefore, it is likely that the data collected accurately reflects the pattern of medication dispensing events.

Measurements

The independent variable is the annual OHA medication adherence for 2008 and 2009, which was measured using a standard approach: the proportion of days covered (PDC). The PDC is an accepted standard measurement for evaluating medication adherence using retrospective data. It is defined as the total number of medication-covered days divided by the number of days in a certain time period. In this study, the annual PDC is calculated as the proportion of days which had at least one OHA available during a 365-day period. Medication history data, including refill date, days of supply, dosage, and frequency, are used to calculate PDC [11]. For patients who took multiple OHAs, we calculated the combined PDC. Non-adherence was defined as a PDC less than 80%, a conventional cut- off point to define poor adherence for chronic conditions [12].

The dependent variables were diabetes hospitalization and all-cause death for 2009 and 2010

(2010 is the most recent year for which death certificate data are available in the INPC). For each patient, we identify whether a diabetes-related hospitalization occurred in 2009 or 2010 according to the primary diagnosis for inpatient admissions in the INPC. Patients who had at least one recorded hospitalization related to diabetes type 2 (ICD-9: 250.*2), cardiovascular disease (ICD-9:410.*. 411.*, 412.*, 414.*), stroke (ICD-9:433.*1, 434.*), or renal disease (ICD-9:585.*) during a study year were considered to have a DM2 related hospitalization. Similarly, the patient's vital status also was identified from the INPC which was previously integrated from the Social Security Administration.

In order to control possible confounders that may influence patient hospitalization and mortality, we examined age, gender, race, income, number of concurrent OHAs (single, multiple), and baseline co-morbidities (hypertension, ischemic heart diseases, stroke, and renal disease) as covariates.

Statistical analyses

Patient OHA adherence was assessed. Descriptive statistics of patient demographic and clinical characteristics, hospitalizations, and mortality were reported for both the adherent and non-adherent groups. Continuous variables were compared using *t*-tests, and categorical variables were compared using $\chi 2$ tests. Generalized linear mixed models (GLMMIX) were performed to evaluate the association between hospitalization or mortality and OHA adherence of the previous year in the INPC DM2 population. Random subject effects were used in these models to accommodate the potential association among observations contributed by the same study subjects. Adjusted odds ratios (OR) were used to quantify the associations. All analyzes were implemented using SAS 9.1 (*SAS Institute, Cary, North Carolina*). Two-sided *p*-values less than 0.05 were considered significant.

Results

A total of 24,067 eligible patients with DM2 were identified for this study from 2008 to 2010, and 35,069 annual PDC were formed. Across the study period, 21,798 (90.6%) of the patients had a mean annual PDC of less than 80%. A total of 4,235 (17.9%) patients had at least one DM2 related hospitalization, and 319 (1.3%) patients died by 2010. Patient characteristics by adherence are outlined in Table 1. Non-adherent patients were relatively younger (60 vs 67), more were female (52% vs. 49%), fewer were white (81% vs 87%), and they had relatively lower income ($45,447 vs $46,872). Around 70% of patients had hypertension in both groups. The rates of hypertension and ischemic heart disease was slightly lower in the non-adherent group, but no significant difference was found for stroke and renal disease between the two groups.

Table 1– Patient characteristics

	Adherent (N=2,269)	Nonadherent (N=21,798)
	N (%)	N (%)
Age at study entry†	67.0 (12.1)	60.4 (15.1)
Female gender	1,114 (49.1)	11,369 (52.2)
Race		
Asian	7 (0.3)	52 (0.2)
African-American	289 (12.7)	3,869 (18.1)
Hispanic	4 (0.2)	158 (0.7)
White	1,969 (86.8)	17,628 (80.9)
Multiple OHA agents	683 (30.1)	6,771 (31.1)
Hospitalization	377 (16.6)	3,945 (18.1)
Death	25 (1.1)	294 (1.3)
Comorbidity		
Hypertension	1,665 (73.4)	15,163 (69.6)
Ischemic heart disease	570 (25.1)	4,893 (22.5)
Stroke	54 (2.4)	536 (2.5)
Renal disease	192 (8.5)	1,669 (7.7)
Median income ($) †	46,872 (9,303)	45,447 (12,654)

† mean (SD)

Table 2– Association between adherence, hospitalization, and death

	Hospitalization		Death	
	Odds Ratio (95%CI)		Odds Ratio (95%CI)	
Non-adherence	1.21	(1.12, 1.31)	1.28	(1.02, 1.61)
Age (10 yr incments)	1.06	(1.02, 1.20)	1.85	(1.10, 1.91
Female gender	1.14	(1.08, 1.31)	0.80	(0.65, 0.95)
Race (ref='White)				
Asian	0.19	(0.06, 0.60)	1.10	(0.16, 8.85)†
African-American	0.79	(0.73, 086)	0.75	(0.59, 0.96)
Hispanic	0.47	(0.29, 0.74)	0.71	(0.17, 2.90)†
Comorbidity				
Hypertension	1.01	(0.94, 1.07)†	0.65	(0.54, 0.79)
Ischemic heart disease	1.82	(1.70, 1.95)	1.24	(1.02, 1.52)
Stroke	1.56	(1.42, 1.71)	2.09	(1.68, 2.89)
Renal disease	1.42	(1.23, 1.64)	2.06	(1.49, 2.89)
Multiple OHAs	0.89	(0.82, 0.92)	0.96	(0.79, 1.15)†
Income ($10,000)	0.99	(0.92, 1.06)†	0.87	(0.82, 0.94)

† *p*-value >0.05

Compared with adherent patients, patients who did not adhere to OHA had significantly higher hospital admission rates (18.1% vs. 16.6%) and higher

mortality (1.35% vs. 1.1%). Table 2 summarizes the results of the GLIMMIX model that analyzed associations between OHA adherence, patient factors and subsequent DM2 related hospitalizations and mortality. After adjusting for patient baseline characteristics, OHA non-adherence is significantly associated with hospitalizations (OR: 1.2; 95% CI [1.1, 1.3]; p<0.0001). Older patients, whites, or patients who had ischemic heart disease, stroke, or renal disease had greater odds of hospitalization. Similarly, OHA non-adherence increased subsequent death due to any cause (OR: 1.3; 95% CI [1.0, 1.6]; p<0.0001). Patient age, male gender, and presence of a co-morbid condition (including ischemic heart diseases, stroke, or renal disease) were also significantly associated with subsequent death. Hypertension had no effect on hospitalization (p=0.84) but was associated with lower risk of death (OR; 0.5; 95% CI [0.54, 0.79]; p<0.001). Multiple OHA use decreased risk of hospitalizations, but had no significant association with death. Patient income had no association with hospitalization, but it was inversely associated with all-cause death.

Discussion

This large, population-based, observational study documented a high prevalence (90%) of non-adherence to OHA in clinical practice. In the multivariable GLIMMIX analyses, after fully adjusting for baseline patient demographic and clinical characteristics, non-adherent patients had a 1.2 fold higher risk for hospitalization with diabetes, cardiovascular diseases, or renal disease in the subsequent year. In addition, we observed significantly increased rates of all-cause mortality (OR: 1.3) among patients who did not adhere to OHA. These findings are consistent with previous population-based studies. Joe Hong, *et al.*, reported that non-adherence to OHA in the first two years increased the risk of hospitalization (OR: 1.26) and death (OR: 1.4) in the third year among patients in a national insurance program [13]; Lau and Nau found a 2.5 times higher risk for diabetes and cardiovascular disease hospitalization among non-adherent patients within one year using a registry [14]; Ho, et al., showed medication non-adherence was significantly associated with all-cause hospitalization (OR: 1.6) and all cause-mortality (OR: 1.8) in 12 months of follow up of an randomized clinical trial [15];

Glycemic control is the primary goal for diabetes management. Oral antihyperglycemic therapies are effective methods to control glycemic levels among patients with type 2 diabetes, thus lowering their risks of developing microvascular and macrovascular complications [16]; Previous studies have shown that OHA adherence was independently associated with HbA1c control: HbA1c decreases 0.10% to 0.16% for each 10% increment in OHA adherence [17]; As a result, improving OHA adherence may lead to better patient health outcomes through better glycemic control. Our study confirmed the importance of OHA adherence in clinical practice. Patients who did not adhere to their OHA medication (PDC less than 80%) were at higher risk of both hospitalization and mortality within one year.

In addition to the therapeutic effectiveness of OHA adherence, good adherence could also be a surrogate for other factors that reflect a high quality of care, healthy behavior, or more effective treatment. Patients who adhere to OHA may be more compliant with other medications, such as HMG-CoA reductase inhibitors and beta-blockers, to better control complications. They may also more actively implement self-management, including monitoring blood glucose levels, following a diet, engaging in regular exercise, caring for their feet, and interacting with providers, which all lead to improved clinical outcomes in diabetes. In contrast, non-adherence may be associated with depression, cognitive impairment, or missed appointments, which may be linked to less than desirable health outcomes.

This study also found that older patients and those with ischemic heart diseases, stroke, and/or renal diseases had higher risks of both hospitalization and death. Interventions for improving medication adherence or other intensive care should target these subgroups so that patients can achieve the full benefits of anti-hyperglycemic therapies. Interestingly, hypertension was not significantly associated with hospitalization and decreased risk of death, which is inconsistent with the notion that hypertension accelerates the progression of both micro- and macro-vascular complications in diabetes. A possible explanation could be that aggressive antihypertensive treatments, including a range of antihypertensive drugs and lifestyle therapies, might be applied to diabetic hypertensive patients to reduce the risk of micro-vascular and macro-vascular disease [18].

Studies about socioeconomic status and patient health outcomes have shown mixed results. Our study found no association between income and hospitalization, while patients with lower income had higher risk of all-cause death. The study subjects are mainly resident in the central Indiana region and have insurance coverage (including Medicaid), with which they might have been provided equal access to the healthcare system. However, low income may directly influence mortality by other context, such as health behaviors, stress, suicide, and homicide, as well as environmental factors [19].

The main findings from this study add evidence to the growing need to establish interventions in medication adherence in order to improve health outcomes for patients with type 2 diabetes. Barriers to medication adherence in diabetes exist at the patient, medication, and provider levels, and a multi-dimensional approach is required to establish efficient interventions. Health HIT and HIE offer the potential to establish such a system. First, objective and data-driven approaches can be programmatically established through an HIE. Second, computerized alerts and reminders can notify pharmacists or prescribers when their patients miss an opportunity to fill a medication in routine clinical practice. Third, predictive modeling may identify patients who are at higher risk of medication non-adherence and may help evaluate specific barriers for these patients. Fourth, widely used Internet and mobile health technologies may empower patients to manage their medications. In addition, a well-established HIE/HIT could support patient-centric and team-based care that better engages patients, providers, and health care systems for improving medication adherence.

Several limitations should be noted. First, the OHA dispensing information was extracted from the Surescript in the INPC covered geographic area; findings may not apply to other population. Second, dispensing claims might not reflect patient medication-taking behavior if patients did not actually use these medications. Nevertheless, filling a prescription is usually consistent with taking the medication. Third, findings from this observational study demonstrated associations (not causations) between OHA non-adherence and hospitalization, as well as associations (not causations) between OHA non-adherence and mortality. Fourth, some patients with type 2 diabetes may use insulin to control their glycemic levels; however, we lack information regarding insulin use for this population. In addition, we were not able to identify the specific cause of death using existing data; therefore, the association between OHA adherence and mortality might be overestimated.

Conclusions

This study found that 90% of patients with type 2 diabetes did not adhere to oral antihyperglycemic agents in clinical practice. Nonadherence was significantly associated with increased risks of hospitalization and death in the following year. The study findings emphasize the importance of improving medication adherence in diabetes management. Developing HIT and HIE strategies should be highly encouraged to effectively intervene with patients and providers regarding medication adherence.

References

[1] Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of diabetes and its burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014.

[2] Hogan P, Dall T, Nikolov P. Economic Costs of diabetes in the US in 2002. Diabetes Care. 2003;26:917-32.

[3] Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL. Prevalence and economic consequences of medication adherence in diabetes: a systematic literature review. Manag Care Interface. 2006 Jul;19(7):31-41.

[4] Mason BJ, Matsuyama JR, Jue SG. Assessment of sulfonylureas adherence and metabolic control. Diabetes Educ. 1995; 21(1):52-7.

[5] Rubin RR. Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus. Am J Med. 2005 May;118 Suppl 5A:27S-34S.

[6] Centers for Medicare and Medicaid Services. Medicare health & drug plan quality and performance ratings 2012 Part C & Part D. 2011;45.

[7] Blumenthal D, Tavenner M. The "meaningful use" regulation for electronic health records. N Engl J Med. 2010 Aug 5; 363(6):501-4.

[8] McClellan M, McKethan AN, Lewis JL, Roski J, Fishere ES. A national strategy to put accountable care into practice. Health Aff (Millwood). 2010 may; 29 (5): 982-90.

[9]. McDonald CJ, Overhage JM, Barnes M, Schadow G, Blevins L, Dexter PR, Mamlin B. The Indiana network for patient care: a working local health information infrastructure. Health Aff (Millwood). 2005 Sep-Oct;24(5):1214–20.

[10] Frisse ME, Tang L, Belsito A, Overhage JM. Development and use of a medication history service associated with a health information exchange: architecture and preliminary findings. AMIA Annu Symp Proc. 2010 Nov 13;2010:242-5.

[11] Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. Am J Manag Care. 2005;11(7):449–57.

[12] Hansen RA, Kim MM, Song L, Tu W, Wu J, Murray MD. Comparison of methods to assess medication adherence and classify nonadherence. Ann Pharmacother. 2009 Mar;43(3):413-22.

[13] Hong JS, Kang HC. Relationship between oral antihyperglycemic medication adherence and hospitalization, mortality, and healthcare costs in adult ambulatory care patients with type 2 diabetes in South Korea. Med Care. 2011 Apr;49(4):378-84.

[14] Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. Diabetes Care. 2004 Sep;27(9):2149-53.

[15] Ho PM, Rumsfeld JS, Masoudi FA, McClure DL, Plomondon ME, Steiner JF, Magid DJ.. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med 2006 Sep 25;166(17):1836-41.

[16] Stratton IM, Adler AI, Neil HA Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000 Aug 12;321(7258):405-12.

[17] Schectman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. Diabetes Care. 2002 Jun;25(6):1015-21.

[18] American Diabetes Association. Standards of medical care in diabetes 2010. Diabetes Care. 2010. 33(Supplement 1); S11-S61.

[19] Lynch J, Smith GD, Harper S, Hillemeier M. Is income inequality a determinant of population health? Part 2. U.S. National and regional trends in income inequality and age- and cause-specific mortality. Milbank Q. 2004;82(2):355-400.

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