Facilitating Clinical Research through the Health Information Exchange: Lipid Control as an Example

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ABSTRACT

Using data from the Indiana Network of Patient Care (INPC), we analyzed long-term statin adherence patterns and their effects on low-density lipoprotein cholesterol (LDL-C) control among patients with type 2 diabetes. Statin adherence was measured by proportion of days covered (PDC) for a 6-month interval prior to each LDL-C test date. Patient demographic and clinical characteristics were used as covariates for LDL-C control and predictors for statin adherence. From 4,350 eligible subjects, 25,596 6-month PDC and LDL-C level pairs were formed between 2001 and 2009. Rates of suboptimal adherence and suboptimal LDL-C control were 68.5% and 46.6%, respectively. Positive predictors for LDL-C control included adherence to statin (OR: 1.87, p<0.0001) and older age (OR: 1.11, p=0.01). Significant risk factors for non-adherence were young age, female gender, African American race and newly-treated status. This study demonstrated the utility of a health information exchange in health outcome and clinical effectiveness research.

INTRODUCTION

One of the challenges for performing health outcome and clinical effectiveness research is assembling the appropriate data particularly when studying a question that involves care in multiple disparate settings. A well-established health information exchange (HIE) supports key components of health outcome research and chronic care management including diabetes.[1] The main features of our HIE infrastructure are as follows: a centrally managed federated data repository; standard medical terminology usage for patient data acquisition; interconnected linkages among different hospitals, laboratories, pharmacies and clinics while maintaining data integrity, quality and security; robust patient matching and patient-centric approaches; capacities augmenting external data resources such as a birth registry and claims data.[2-3] The rich health information and data integration of the HIE enable generating aggregated, complete, accurate and longitudinal patient data across different health care facilities over time. In addition, the nature of multidirectional communication of the HIE ensures easy dissemination with the experience and knowledge gained from research.

Hyperlipidemia has a high prevalence in type 2 diabetes and causes high rates of macrovascular complications. Up to 80% of patients with type 2 diabetes will develop or die of macrovascular diseases.[4] In order to control macrovascular risk factors among patients with type 2 diabetes for both primary and secondary prevention, the American College of Physicians (ACP) recommended widespread statin (3-HYDROXY-3-METHYL-glutaryl coenzyme A [HMG-CoA] reductase inhibitor) use to lower serum cholesterol, with a target low-density lipoprotein cholesterol (LDL-C) level of 100mg/dL.[5]

Despite the known high macrovascular risks and the evidence-based guidelines for vascular protection, suboptimal lipid control is widely observed among patients with type 2 diabetes in clinical settings.[6] Clinical trials have analyzed statin adherence patterns and have found a significant correlation between adherence to statins and LDL-C reduction.[7-8] However, these studies usually follow patient medication taking behavior for only a short time period, while medication adherence changes over time especially for patients with chronic conditions. In addition, patients in a usual-care setting often do not adhere to prescribed treatment regimens and regular LDL-C laboratory tests as closely as those in a clinical trial. Medication non-adherence to statins has been demonstrated to be a barrier for patients in usual care settings to obtain benefits from statins.[9] These discrepancies suggest that a longitudinal study of real-world clinical settings is necessary to compare the magnitude of benefits of statin therapy to that which is demonstrated in clinical trials.

Research on medication adherence and health outcomes fundamentally relies on complete patient data including medication history and laboratory test results. Patients, especially with chronic conditions, often receive care from different health care facilities, and patient data are usually scattered across different "islands". It is impossible to generate complete patient-level data from multiple sources without support of an HIE. In addition, compared with pill counts, self-reporting, and questionnaires, objective and data-driven approaches which can be programmatically established through the HIE are more accurate and becoming increasingly important for research related to medication adherence.

Furthermore, the linkage between patient medication data and laboratory records allows investigation of patient behavior and therapeutic effects with easy access and at relatively low cost.[10]

In this present observational study, using longitudinal patient medication and laboratory data from our local operational HIE, we first analyzed the association between patient LDL-C control and statin adherence. We further investigated potential risk factors for non-adherence to statins. We hypothesize that this study will provide insight into medication taking behavior among patients with type 2 diabetes and its effects on lipid control in real-world clinical settings.

METHODS

Data Sources and Settings

For purposes of this analysis, we extracted information from the Indiana Medicaid data system which contained demographic, diagnosis, and treatment information over time. The prescription records, including refill dates, days of supply, dose, and frequency, were retrieved for all statins. Patient LDL-C test results were retrieved from the Indiana Network of Patient Care (INPC). The INPC is an operational regional clinical informatics network that has served five major hospital systems (55 hospitals and more than 100 geographically distributed clinics) across Indiana for more than ten years. This system delivers medical record information from hospitals, laboratories, imaging centers, pharmacies and physician offices including registration records, laboratory tests, radiology reports, diagnoses, and administrative data.[2-3] Laboratory test results are mapped to LOINC codes, and patients' multiple medical records are linked through a robust linking algorithm. For this study, patient medication information that Regenstrief obtains from Indiana Medicaid was linked to the INPC aggregated patient LDL–C laboratory data. All patient identifiers were removed before data analysis in order to protect confidentiality. This study was approved by the Institutional Review Board of Indiana University and the INPC Management Committee.

Eligibility Criteria

Study subjects were age 18 to 65 years during the time period of 2001 to 2009, 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, and had at least one pharmacy claim for a statin identified by the First DataBank *Standard Therapeutic Code* system (STC: B937, C221, C227, C229) during the same study period. Women with gestational diabetes were excluded. To be included in the cohort, the patient had to have at least one LDL-C test result from the INPC and at least one pharmacy claim for a statin prior to the LDL-C test date.

Measurements

We calculated patient statin adherence using a standard measurement: proportion of days covered (PDC). The PDC focuses on persistence or continuation at the time of prescribed treatment. It is defined as the total number of medication covered days divided by the number of days in a certain time period. Claims data, including refill dates, days of supply, dose, and frequency, are used to calculate PDC.[11] To dynamically and accurately reflect the effect of statin adherence on LDL control, we defined the LDL-C test date as the index date and then traced back the patient medication adherence for six months prior to this index date. Since statin medications are considered interchangeable, drug switching or dose changing did not count as a different filled prescription. Using a validated classification cut-off point,[12] adherence to statins was categorized into two levels: 1) Adherent to statins if 6-month PDC was equal or greater than 80%. 2) Non-adherent to statins if 6-month PDC was less than 80%.

Patient serum LDL- C was used as the dependent variable and retrieved from the INPC using a set of standard laboratory test terminologies that were mapped to the LOINC codes 13457-7 and 18262-6. According to standard guidelines, we classified LDL-C results into two categories: controlled (less than 100mg/dL) or not-controlled (equal or greater than 100mg/dL).

Other potential covariates were selected based on previous type 2 diabetes management studies. We extracted patient demographic and clinical information such as age, gender, race and duration of statin treatment. These factors were used to control the possible confounders in the analysis of association between statin adherence and LDL-C control and also were applied as predictors for statin adherence.

Statistical Analysis

Descriptive statistics of patient characteristics, adherence to statins, and the average LDL-C level of different subgroups were reported. The associations between statin adherence and dichotomized LDL-C control were examined using logistic regression models. To accommodate the potential correlation of repeated measures of LDL-C laboratory results and statin adherence of one subject, we used the generalized estimating equation (GEE) model with clustered symmetric correlation structures. Odds ratios (OR) were reported to quantify the magnitude

of the association. All analyses were implemented using SAS 9.1 (*SAS Institute, Cary, North Carolina*). Statistical significance was set at an accepted alpha of $p<0.05$.

RESULTS

A total of 4,350 subjects were identified, and 25,596 of 6-month PDC and LDL-C level pairs were formed across the study period. The LDL-C levels ranged from 50 to 248mg/dL with an average of 108.62 mg/dL (SE: 0.23mg/dL). Across the study period, about 68.5% of the patients had a mean 6-month PDC of less than 80%, and 46.6% of patients had an average LDL-C greater than 100mg/dL. Patient characteristics are outlined in Table 1. The average entry age of study subjects was 49 years, and 64.7% of the subjects were female. The majority of the subjects were non-Hispanic Whites (66.8%). 56% of the subjects had been treated with statins for three years or less. Compared with non-adherent patients, patients who were adherent to statin therapy had significantly lower average LDL-C levels among different patient subgroups.

After controlling for demographic and clinical factors, patients adherent to statins were more likely to achieve optimal LDL control (OR: 1.87 [95% CI: 1.67-2.10], $p<0.0001$). Increased age was also related to better LDL-C control (OR: 1.11 [95%CI: 1.02-1.20], $p=0.01$). Females were less likely to achieve optimal LDL-C control (OR: 0.69 [95% CI: 0.59-0.80], $p<0.0001$). Race and duration of treatment had no effects on LDL-C level (Table 2.).

Six predictors of adherence analyzed by the GEE model are shown in Table 3. Four of them achieved statistical significance ($p<0.001$). Older age and duration of statin treatment were positive predictors. Female gender and African American race were negative predictors. The effects of Hispanic or other races on statin adherence could not be assessed.

DISCUSSION

Aggregate health data from an HIE offers valuable opportunities for health outcome research.[13] First, data normalization using standard terminologies, one core component of the HIE, enables interoperability of different health data resources and additionally provides rapid information retrieval for population-based studies. Second, observational studies conducted from the large longitudinal HIE databases have many advantages: speed, real-world decisions, and low cost, while providing comparative knowledge to that of clinical trials, especially for research about chronic conditions.[14] Our study is one example.

According to longitudinal data from our local operational HIE, 31.5% of the patients were classified as adherent to statins and 53.4% had optimal LDL levels (less than 100mg/dL) which parallels data from other population-based studies.[15-16] However, these numbers are much lower than results from clinical trials and disease management programs with a rate of up to 96% for statin adherence and 70% for optimal LDL control.[8,17] Despite the evidence of effectiveness of statins in lowering cholesterol and ultimately reducing vascular complications in trials, lack of statin adherence in real world settings may limit the success of statins in controlling lipid levels.

Our primary analysis showed that patients who adhere to statins are 1.87 times more likely to achieve optimal LDL-C control compared to patients who were non-adherent to statins. This finding is consistent with conclusions from other studies that non-adherent patients are less likely to reach target

Table 1. LDL-C levels in study subjects

Factors	Number of Subjects (%) (n=4,350)	Mean LDL (mg/dl) (95% Confidence Interval) Non_adherent patients	Adherent patients
Demographics			
Age (year) Mean= 49			
18-30	160 (3.68%)	108.11 (104.35-111.86)	96.38 (91.47-101.30)
30-40	597 (13.72%)	106.69 (104.77-108.61)	96.11 (93.21-99.01)
40-50	1,414 (32.51%)	105.13 (103.99-106.26)	95.74 (94.08-97.40)
50-64	2,179 (50.09%)	105.36 (104.53-106.19)	93.59 (92.71-94.48)
Gender			
Female	2,815 (64.71%)	108.17 (107.41-108.93)	95.65 (94.74-96.57)
Male	1,535 (35.29%)	99.77 (98.73-100.81)	91.88 (90.61-93.15)
Race			
African Americans	1,310 (30.11%)	108.82 (107.67-109.96)	94.39 (92.88-95.90)
Hispanic	67 (1.54%)	108.17 (102.39-113.96)	105.19 (95.46-114.92)
Other	66 (1.52%)	98.71 (92.12-105.29)	90.29 (81.28-99.31)
White	2,907 (66.83%)	104.03 (103.28-104.77)	94.19 (93.32-95.05)
Clinical Characteristics			
Duration of Statin Treatment (year)			
0-3	2,436 (56.00%)	104.07 (103.11-105.04)	96.57 (95.04-98.11)
3-6	1,421 (32.67%)	107.33 (106.34-108.33)	93.47 (92.39-94.56)
6-9	493 (11.33%)	105.19 (103.82-106.56)	93.18 (91.87-94.49)
Overall		105.66 (104.94-106.39)	93.34 (92.44-94.28)

lipid values and subsequently less likely to achieve benefits from therapy. Young age and female gender are risk factors for uncontrolled LDL-C in our study, which are consistent with findings from other studies. Many studies conclude that African Americans with diabetes are at higher risk of uncontrolled health outcomes including elevated LDL-C. Surprisingly, race was not significantly related to LDL-C control in our study after adjustment for other factors. One prior investigation emphasized that racial disparity in diabetes outcomes is mainly due to sociodemographic factors, while clinical factors, such as body mass index, explained little to no difference.[18] Our study population was composed entirely of Medicaid members, and majority subjects geographically located in the central Indiana. Sociodemographic difference in this population may not be sufficient to detect the difference of patient LDL-C control. Future research on racial disparity and LDL-C control should use resources with more diverse sociodemographic information, such as the existing array of different health care payer data in the INPC.

Our secondary analysis indicates that risk factors for non-adherence to statins are young age, female gender, African American race, and newly-treated status. These risk factors are consistent with the results from most studies of medication adherence. One study found that the hazard of discontinuation of statins was high in the first six months of therapy, but little is known about long-term adherence patterns.[19] Our study found that increased duration of treatment (units in 3 years) is significantly related to optimal adherence to statins, and patient tend to be more adherent if they have been kept statin therapy for a long time period. One similar study confirmed that adherence to statins declines sharply in the first six months of treatment and continually declines more slowly over five years, but then increased slightly at 10 years.[20] Interventions designed to improve adherence to statin should focus on high-risk groups and early initiation.

Table 2. Effects of statin adherence and patient characteristics on LDL-C control

Predictors	Odds Ratio (95% CI)	*p*-value
Adherence	1.87 (1.67-2.10)	<0.0001
Age (10 years)	1.11 (1.02-1.20)	0.0108
Gender		
Female	0.69 (0.59-0.80)	<0.0001
Male	-- --	
Race		
African Americans	0.89 (0.78-1.03)	0.1156
Hispanic	0.78 (0.47-1.28)	0.3307
Other	1.55 (0.83-2.88)	0.1675
White	-- --	
Duration of Treatment	1.04 (0.95-1.14)	0.3684

Table 3. Effects of patient characteristics on statin adherence

Predictors	Odds Ratio (95% CI)	*p*-value
Age (10 years)	1.31 (1.18-1.44)	<0.0001
Gender		
Female	0.75 (0.65-0.87)	<0.0001
Male	-- --	
Race		
African Americans	0.68 (0.58-0.79)	<0.0001
Hispanic	0.69 (0.43-1.12)	0.1382
Other	1.16 (0.73-1.85)	0.5242
White	-- --	
Duration of Treatment	1.53 (1.41-1.67)	<0.0001

This study has some limitations. First, the statin dispensing information only came from the Medicaid program, thus the calculated adherence of statins may not be accurate. This is because statin dispensing information from other health insurance plans may not be included. However, because Medicaid covers the cost of prescribed statins, it is likely that few Medicaid members under age 65 use other insurance plans. 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.[21] Third, we did not study specific statin individually because all statins have the same active chemical ingredient and belong to same therapeutic class. However, adherence and therapeutic effects may vary for different statin types. Since we do have related information available, an additional investigation could be conducted to provide more detailed information to aid provider selection of statins that are effective for LDL-C control and easier patient adherence.

CONCLUSION

Using lipid control for patients with type 2 diabetes as an example, the present study demonstrated that health outcome and clinical effectiveness research can be successfully performed through an HIE. This study not only confirmed that better adherence to statins leads to better lipid control for patients with type 2 diabetes, but also identified risk factors for suboptimal LDL-C control and non adherence to statins. Additionally, it provided important information about the discrepancy in findings between research and clinical settings. Since the INPC is incorporating more commercial claims-based and pharmacy dispensing data from large health insurers and pharmacy benefit consortia, more health outcome research can be performed by linking these data resources with laboratory test

records from the INPC. Further, the low rates of adherence and LDL-C control observed in our study indicate that there is a great need to develop a systemic approach to ensure patient adherence in routine clinical settings. The HIE provides an excellent platform to develop such a system that can assess patient medication adherence and can encourage providers to monitor patients' ongoing adherence status for diabetes as well as other chronic conditions. Future work will focus on leveraging this information in clinical practices and defining effective interventions for physicians and patients to improve medication adherence and ultimately improve health outcomes.

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