At a Glance

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Outcomes Associated With Primary and Secondary Nonadherence to Cholesterol Medications

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ABSTRACT

Objectives: To examine the impact of primary nonadherence (PNA) and secondary nonadherence (SNA) to cholesterol medication on clinical outcomes.

Methods: This retrospective cohort study used electronic medical record data from a large managed care organization, and includes patients newly prescribed cholesterol medication(s) between December 1, 2009, and February 28, 2010. The date the prescriber ordered the initial cholesterol prescription was defined as the index date. Patients were required to be aged at least 18 years, and have continuous pharmacy benefits for 12 months before and 18 months after the index date. PNA was defined as failure to fill the initial prescription within 180 days of the index date. SNA was defined as having a medication possession ratio of <80%. Study outcomes included changes in low-density lipoprotein (LDL) values from baseline, emergency department (ED) visits, and hospitalizations.

Results: Of the 13,415 patients included in the study, 10% were primary nonadherent and 53% were secondary nonadherent to their cholesterol medication. After adjusting for patient and physician characteristics, post index LDL values in primary and secondary nonadherent patients were significantly higher than in adherent patients by 41 mg/dL and 24 mg/dL, respectively. Risk of ED visits was significantly higher among primary and secondary nonadherent members relative to adherent members (hazard ratio [95% CI]: 1.25 [1.04-1.50] for PNA; 1.28 [1.15-1.43] for SNA).

Conclusions: Better primary and secondary adherence was directly related to improvements in short-term clinical outcomes. This study provides evidence that clinical interventions should target both primary and secondary nonadherent patients in a timely fashion.

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Primary nonadherence (PNA) is defined as the failure to fill the initial prescription, whereas secondary nonadherence (SNA) refers to patients taking insufficient doses required to experience a therapeutic effect, missing doses or discontinuing therapy early. Although SNA can be easily measured using pharmacy claims data, PNA has only recently become more readily observable with the increased availability of the electronic medical record (EMR). Nearly half of all patients on chronic medications are secondary nonadherent and an estimated 20% of patients discontinue therapy after the first prescription.[1,2] In addition, an estimated 20% to 35% of patients are primary nonadherent, depending on the medication class.[3,4]

Most medication nonadherence research has focused on risk factors associated with SNA, while identified risk factors of PNA have only begun appearing in the literature.[3] However, the association between PNA and clinical outcomes is relatively unknown compared with the association between SNA and clinical outcomes.[5-8] Furthermore, the impact of PNA on clinical outcomes relative to SNA has not yet been quantified. The challenge with evaluating the relationship between adherence and clinical outcomes is the potential of unobserved confounders that may bias study results. Adherent patients may also be more likely to exercise regularly, eat better, and participate in other health-promoting activities.

The objective of this study was to evaluate the impact of PNA and SNA to cholesterol medication on clinical outcomes, such as changes in low-density lipoprotein (LDL), emergency department (ED) visits, and hospitalizations. This study used EMR data from a large, integrated health plan and included electronic prescribing data. Using the rich pharmacy and medical claims data and laboratory data available in EMR data should offer better insight into the effects of PNA and SNA, insight that is less likely to be confounded by unobserved differences across adherence groups.

METHODS

Study Design and Setting

This retrospective cohort study was conducted at a large managed care organization providing comprehensive healthcare

to an estimated 3.4 million current members at its 14 medical centers located throughout Southern California. The internal institutional review board approved this study. The majority of healthcare services and prescriptions are provided to members within its integrated system. Prescriptions are entered into the EMR system and this information is electronically sent to the pharmacy, including information identifying the prescribing physician. Once the patient checks in at the pharmacy, the prescription is released from the queue and filled while the patient waits.

The EMR also includes data on patient demographics, outpatient and inpatient diagnoses, procedures, laboratory results, and prescription records. Geocoded socioeconomic data based on census-track data are also available in the patient's EMR. Data on the characteristics of the prescribing physician are also available within the data system.

PRACTICAL IMPLICATIONS

This study uses pharmacy and medical claims data and laboratory results to demonstrate the relative impact of primary and secondary nonadherence to cholesterol medication on short-term clinical outcomes of low-density lipoprotein (LDL) levels, emergency department (ED) visits, and hospitalizations.

- Both primary nonadherence and secondary nonadherence to cholesterol medications are considerably high at 10% and 53%, respectively.
- Relative to adherent patients, both primary and secondary nonadherent patients achieve smaller decreases in LDL levels and experience higher risk of ED visits.
- Clinical adherence interventions should target both primary and secondary nonadherent patients in a timely fashion.

Inclusion and Exclusion Criteria

This study included all new prescriptions generated by the e-prescription system for any cholesterol medication prescribed between December 1, 2009, and February 28, 2010. A new prescription was defined as the patient having no prior fills for any cholesterol drug during the 12 months before the date the prescription was ordered (index date). Patients were required to be aged at least 18 years on the index date and have continuous membership and drug benefits for 12 months before and 18 months after the index date. In addition, patients must have had at least 1 LDL laboratory value within 12 months both before and after the index date.

Since only prescriptions generated by the e-prescribing system were included, renewed prescriptions, transfers from outside pharmacies, verbal orders, prescriptions printed out as a hard-copy prescription in the doctor's office, and hard-copy prescriptions from outside providers were excluded. Prescriptions that were later cancelled by the prescriber before it was picked up by the patient were also excluded. However, filled prescriptions discontinued by the physician due to emerging clinical concerns could not be differentiated from patient-initiated discontinuations. Lastly, statins are the most commonly prescribed cholesterol medication and are contraindicated during pregnancy. Thus, any prescriptions written for female patients who became pregnant (based on gestation date) during the study period were excluded.

Adherence Measures

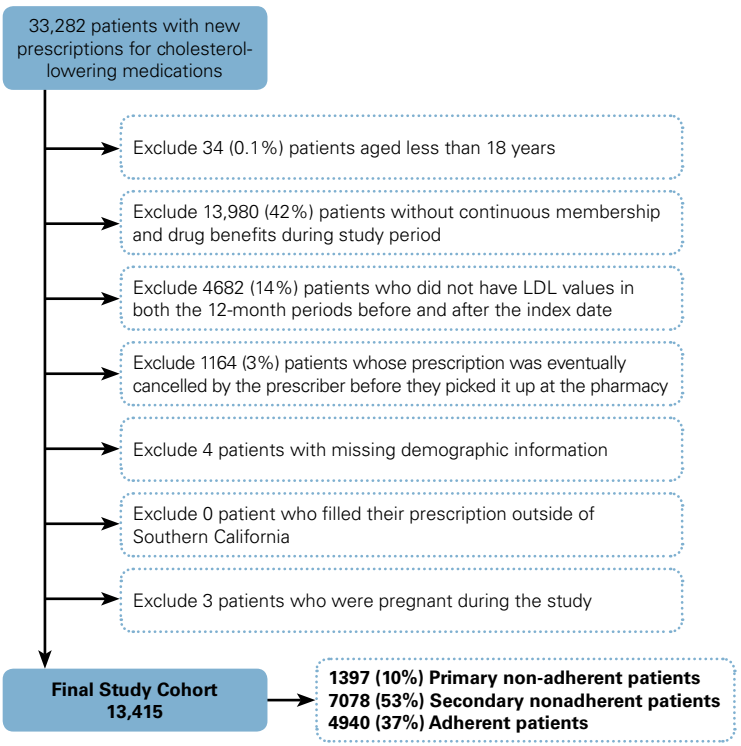
To evaluate the association between adherence and LDL values, patients were classified into 1 of 3 mutually exclusive groups: primary nonadherent, secondary nonadherent, and adherent. Primary nonadherent patients were defined as those who failed to fill their new cholesterol prescription within 180 days of the index date. Even if a patient eventually filled their prescription on day 181, they were still considered as primary nonadherent. Based on descriptive results from previous work, more than 99% of patients who eventually filled their first cholesterol prescription filled it within 180 days.[2] Thus, extending past 180 days would not lead to any significant changes.

Secondary adherence was measured in primary adherent patients using the medication possession ratio (MPR), which is an appropriate measure for adherence to medications used to treat chronic conditions. The MPR was calculated as the total days supplied for any cholesterol medication during the 12-month period after the index date divided by 365 days. MPR was truncated so that it could not be below 0 or above 1. Patients were considered secondary nonadherent if MPR was <80%, a cutoff commonly used in other studies.[5]

Study Outcomes

The primary outcome in this study was change in LDL laboratory values from baseline. Baseline LDL was defined as the most recent LDL value during the 12-month period prior to the index date. The average LDL value during the 12-month period after the index date was used to calculate the change in LDL from baseline. Secondary outcomes included ED visits and hospitalizations (all-cause), which were examined between 12 and 18 months after the index date. This allowed for a "run-in" period in which the medications were given time to have impact before effects on utilization were measured. The length of the run-in period of 12 months was based on evidence from randomized controlled trials that have previously shown that beneficial effects of statins begin 1 to 2 years after initiation.[9-14]

Figure 1. Identification of Study Cohort



LDL indicates low-density lipoprotein.

Study Covariates

Patient characteristics included age at index date, gender, race/ethnicity, median household income, and insurance characteristics (Medicare, Medicaid, commercial, primary subscriber, dual coverage). A 2-year period (1 year prior to and 1 year after the index date) was used to measure baseline health status variables, which included baseline LDL level, a weighted Charlson comorbidity index (CCI) score, and prior healthcare utilization (prescription count, clinic visit count, ED visits, hospitalizations). An indicator was also created for patients who switched or augmented their index cholesterol medication after the index date, since these patients are likely to differ from patients who were maintained on initial therapy. Prescriber characteristics included gender, age at index date, race/ethnicity, and specialty (internal medicine, pediatrics, urgent care, ED). Observations with missing data for these variables were grouped as "unknown."

Statistical Analysis

Baseline patient characteristics were compared among the 3 patient adherence groups using ANOVA. Average lab values were plotted over time by adherence group to track trends in LDL values. The paired *t* test was used to test whether the average change in LDL value before and after the index date was statistically significant for each patient adherence group.

Several multivariate statistical methods were employed to develop a more complete picture of the impact of adherence on outcomes. Linear multivariable regression was used to estimate the association between adherence level and change in post index LDL values, controlling for all patient and prescriber characteristics except for baseline LDL. Time to ED visit or hospitalization was analyzed using multivariate Cox proportional hazard models to evaluate the risk of these events relative to the adherent patient group, while controlling for all patient and prescriber characteristics, including baseline LDL. Patients were followed until the event occurred and censored from the analysis at the end of the follow-up period. We also estimated the impact of average post index LDL levels on time to ED or hospital visits using Cox proportional hazard models. Sensitivity analysis was performed using the last LDL lab result and changes in LDL from baseline, rather than the average value during the post index period.

For all analyses, a significance level of .05 was considered as statistically significant. All statistical analyses were performed using the SAS statistical package version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 13,415 patients satisfied inclusion and exclusion criteria (Figure 1). Overall, 1397 patients (10%) were primary nonadherent to their cholesterol medication, 53% were secondary nonadherent (MPR <80%), and 37% were adherent. Nearly two-thirds of primary adherent patients filled their cholesterol medication on the day it was written. Among secondary nonadherent patients, 2394 (33.8% of the secondary nonadherent group) filled only the very first prescription—never getting any refills—during the 12-month follow-up period.

Comparisons of baseline patient characteristics revealed significant differences among adherence groups (Table 1). On average, adherent patients were the oldest and sickest in comparison with nonadherent groups; these adherent patients were more likely to be prescribed cholesterol medications for secondary prevention, and to have higher CCI scores and baseline LDL values. Furthermore,

adherent patients were more likely to switch or augment therapy after the index date, indicating they may have been more difficult to treat. Lastly, adherent patients were significantly more likely to be on 1 or more non-cholesterol prescription medications and to have more clinic visits, ED visits, and hospitalizations. Secondary nonadherent patients were healthier than adherent patients but sicker than primary nonadherent patients at baseline. Thus, those who stood to gain the most benefit from taking their cholesterol medication were most likely to do so.

During the 12-month period before the index date, the average (SD) number of LDL tests per patient in the primary nonadherent, secondary nonadherent, and adherent patient groups was 1.87 (0.99), 1.75 (0.95), and 1.77 (0.94), respectively (P <.0001). The average (SD) number of LDL tests per patient increased during the 12-month period after the index date for all 3 patient groups: 2.31 (1.42) for primary nonadherent, 2.63 (1.52) for secondary nonadherent, and 2.75 (1.40) for adherent, P <.0001 for all. With respect to the timing of the labs, all 3 patient groups had spikes in LDL lab testing during the first 6 months after the index date, and then plateaued by 7 months after the index date.

The relative impacts of PNA and SNA on LDL values are best illustrated in **Figure 2**. The LDL levels drop for all 3 patient groups, even patients who never filled their prescription for a cholesterol drug. The impact of adherence is measured by the difference in the 3 plots. Patients who filled at least 1 prescription achieved a larger drop in LDL in month 1 and patients who were compliant over time exhibited a larger drop in month 1 than patients who eventually discontinued therapy.

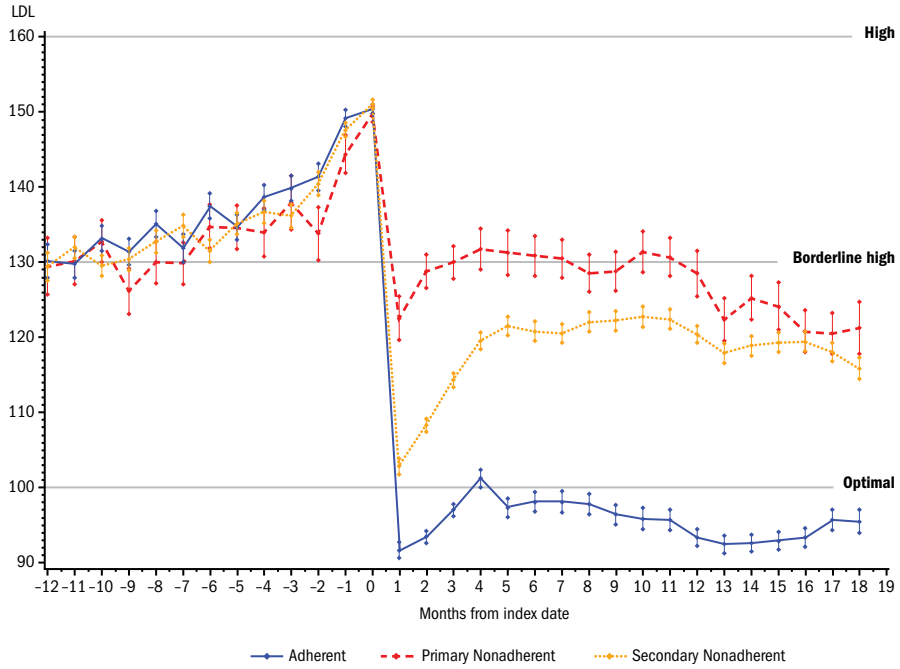
Table 1. Comparison of Baseline Patient Characteristics

Characteristic	Primary nonadherent (n = 1397)	Secondary nonadherent (n = 7078)	Adherent (n = 4940)	*P* value
Male (%)	688 (49.3%)	3511 (49.6%)	2478 (50.2%)	NS
Mean age in years (SD)	57.2 (12.7)	56.7 (12.7)	60.5 (12.2)	<.0001
Race or ethnicity (%)				<.0001
White	641 (45.9%)	2725 (38.5%)	2826 (57.2%)	
Hispanic	446 (31.9%)	2783 (39.3%)	1205 (24.4%)	
Black	160 (11.5%)	834 (11.8%)	381 (7.7%)	
Asian/Pacific Islander	143 (10.2%)	699 (9.9%)	505 (10.2%)	
Multi-racial	7 (0.5%)	24 (0.3%)	16 (0.3%)	
American Indian /Alaskan Native	0	13 (0.2%)	7 (0.1%)	
Patient household income				<.0001
$22,000 or less	7 (0.5%)	70 (1.0%)	25 (0.5%)	
$22,000 to $45,000	654 (46.8%)	3506 (49.5%)	1970 (39.9%)	
$45,000 to $55,000	272 (19.5%)	1532 (21.6%)	1120 (22.7%)	
$55,000 or more	413 (29.6%)	1717 (24.3%)	1663 (33.7%)	
Unknown	51 (3.7%)	253 (3.6%)	162 (3.3%)	
Secondary prevention (%)	435 (8.8%)	80 (5.7%)	428 (6.1%)	<.0001
Subsequent use of other cholesterol medications after index date (%)	4 (0.3%)	676 (9.6%)	557 (11.3%)	<.0001
Average (SD) Charlson comorbidity index score	1.2 (1.9)	1.4 (1.9)	1.5 (2.0)	<.0001
Average (SD) prescription count in prior year	5.4 (4.8)	7.2 (5.5)	7.7 (5.6)	<.0001
Average (SD) clinic visit count in prior year	6.7 (7.0)	7.6 (7.8)	7.9 (8.1)	<.0001
ED visit in prior year	436 (31.2%)	2507 (35.4%)	1710 (34.6%)	<.05
Hospitalization in prior year	253 (18.1%)	1535 (21.7%)	1288 (26.1%)	<.0001
Medicare insurance	365 (26.1%)	1700 (24.0%)	1735 (35.1%)	<.0001
Medicaid insurance	3 (0.2%)	60 (0.9%)	21 (0.4%)	<.01
Commercial insurance	1380 (98.8%)	6993 (98.8%)	4895 (99.1%)	NS
Primary subscriber	1083 (77.5%)	5232 (73.9%)	3797 (76.9%)	<.01
Dual coverage (from spouse)	24 (1.7%)	165 (2.3%)	123 (2.5%)	NS
Patient's average baseline LDL value	146.3 (36.0)	148.8 (38.2)	149.4 (37.2)	<.05

ED indicates emergency department; LDL, low-density lipoprotein; NS, not significant.

Over the 12-month period following the index date, average LDL value measured over the post period continued the pattern of response immediately following the patients' index dates. Adherent patients achieved the largest drop in average LDL, followed by patients who did not achieve an 80% MPR and patients who failed to fill their initial prescription. The average (SD) reductions in LDL over the post index period were 14.2 (27.2), 32.3 (35.8), and 55.7 (33.4) mg/dL, among patients in the primary nonadherent, secondary nonadherent, and adherent group, respectively (**Table 2**). The average change in LDL from baseline was significantly different from 0 for all adherence groups (P <.0001). When comparing the changes in LDL across 3 adherence groups, results were significantly different (P <.0001). For all groups, LDL levels decreased most rapidly during the first 3 months after the index date, and increased slightly to a steady level after 4 months (Figure 2). After adjusting for observed patient and prescriber

Figure 2. Average Low-density Lipoprotein (LDL) Values Over Time by Adherence Group



characteristics, post index LDL values in primary nonadherent and secondary nonadherent patients were still significantly higher than in adherent patients by about 41 and 24 mg/dL, respectively (P <.05).

During the 12 to 18 months after the index date, the rate of ED visits in the primary nonadherent, secondary nonadherent, and adherent groups was 11.0%, 13.3%, and 11.4%, respectively (P <.01). The rate of hospitalization was not significantly different among the 3 adherent groups (6.7% for primary nonadherent, 7.1% for secondary nonadherent, and 7.6% for adherent).

Table 3 reports the results of the various multivariate analyses conducted to trace the impact of adherence on hospitalizations and ED visits. The rate of hospitalizations is 7.3% over the post period while the rate of ED visits is slightly higher at 12.4%. PNA and SNA do not have statistically significant impacts on the risk of hospitalizations, though the point estimates are consistent with increased risk. However, nonadherent patients do exhibit a higher risk of an ED visit, relative to adherent patients. Lastly, the LDL level that was achieved post treatment, whether measured using the average or last LDL value, had no impact on the risk of hospitalizations or ED visits. Also, the magnitude of the LDL change from baseline appears to impact the risk of hospitalization (P <.10) but had no impact on ED risk.

DISCUSSION

This study used a large EMR database to confirm that better primary and secondary adherence to statin therapy is significantly associated with clinically meaningful reductions in LDL levels. In this study population, 10% of patients were primary nonadherent and another 53% were secondary nonadherent. The PNA rate to cholesterol medication in this study is similar to that found by other studies set in integrated settings where pharmacies are located near the primary care facility.[15]

On average, LDL levels fall by 56 mg/dL within the first 3 months of starting therapy and remain at those levels if the patient adheres to treatment. Despite not initiating cholesterol therapy, primary nonadherent patients

Table 2. Comparison of LDL Values Among Adherence Groups During 12-Month Follow-up Period

	Primary nonadherent (n = 1397)	Secondary nonadherent (n = 7078)	Adherent (n = 4940)	*P* value
Average (SD) baseline LDL value (most recent value)	146.3 (36.0)	148.8 (38.2)	149.4 (37.2)	<.05
Average (SD) LDL value during 12-month follow-up period	132.1 (34.5)	116.6 (35.3)	93.8 (27.1)	<.0001
Average (SD) change in LDL value within a patient[a]	–14.2 (27.2)	–32.3 (35.8)	–55.7 (33.4)	<.0001

[a]The paired *t* test reveals whether average change within a patient was significantly different from 0.
LDL indicates low-density lipoprotein.

Table 3. Estimated Hazard Ratios for Measures of Adherence and Impact on LDL

	N = 13,415	
Nonadherence (vs adherence)	Hospitalizations N = 973	ED Visits N = 1662
Primary nonadherence	1.14 (0.90-1.43)	1.25 (1.04-1.50)
Secondary nonadherence	1.04 (0.91-1.20)	1.28 (1.15-1.43)
Change in average LDL from baseline (per mg/dL)	0.998 (P = .0884)	1.00 (P = .5267)
Change in last LDL from baseline (per mg/dL)	0.998 (P = .0611)	1.00 (P = .8095)

All models above were controlled for patient characteristics (age, gender, race/ethnicity, median household income, insurance characteristics, weighted Charlson comorbidity index score, prior healthcare utilization) and prescriber characteristics (gender, age, race/ethnicity, specialty).

also had an initial drop in LDL. This immediate drop in LDL seen across all patient adherence groups indicates a shared response across all patients of becoming aware of their elevated LDL. These patients may potentially have decreased their LDL levels via lifestyle changes in diet and exercise, and the diagnosis of hyperlipidemia, along with being prescribed a new cholesterol medication, may have been the "wake-up call" these patients needed to change their health behavior. It is also possible that the baseline LDL level was not initially measured accurately (eg, nonfasting) and the level decreased after treatment was prescribed due to patient compliance with pre-test fasting in the post period. Another potential reason for the initial drop in LDL could be regression to the mean. As such, healthcare providers may consider repeating an LDL test prior to starting long-term cholesterol treatment.

Recent changes in national treatment guidelines for cholesterol have shifted focus from targeting LDL levels to prescribing fixed statin doses to achieve an average LDL reduction by 30%-50% with moderate-intensity statins or >50% with high-intensity statins.[16] The results from this study reveal that on average, PNA patients do not achieve the same LDL level reductions as adherent patients. They also experienced an increased risk of ED visits similar to SNA patients. This suggests that clinical interventions aimed at decreasing cholesterol levels should target both PNA and SNA.

The relative LDL reductions achieved by each patient group in Figure 2 provides more real-world evidence that statins really do work if patients are adherent to their cholesterol medication. Thus, healthcare providers may monitor LDL to detect PNA or SNA if refill data are not readily available to them. If EMR data are available, they should be utilized to intervene early; follow-up lab tests within the first 3 months of drug initiation can confirm that the patient is adherent. Due to their low cost, a simple blood test and/or claims review may potentially be cost-effective ways to identify PNA patients for interventions and to improve patient health. Furthermore, as electronic prescribing becomes ubiquitous within the next several years, it will become easier to identify PNA patients and intervene within 2 weeks.

The observed difference in baseline characteristics across the PNA, SNA, and adherent patient groups reinforces the potential for unobserved differences in health status and health behavior impacting the estimated effects of adherence, providing evidence that patients who would benefit the most from statin therapy were more likely to be adherent. Although primary and secondary nonadherent patients had comparable LDL levels to those of adherent patients, nonadherent patients had fewer risk factors than adherent patients (fewer patients taking cholesterol medications for secondary prevention and fewer comorbidities). As such, it appears that PNA and SNA patients do not see the benefits of drug therapy as acutely as adherent patients, and unobserved differences among adherence groups likely exist in terms of healthy behaviors. However, it is unlikely that unobserved differences would change over relatively short timeframes. Thus, the improvements in short-term clinical markers (eg, LDL) found in this study are likely directly attributed to adherence behavior rather than other unobserved health behaviors correlated with adherence. Furthermore, since adherent patients are sickest, followed by secondary nonadherent and primary nonadherent patients, results on ED visits and hospitalizations are biased against finding an effect, and any statistically significant difference across the patient groups would be meaningful given it is a lower bound estimate.

In contrast to prior work that evaluates the association between adherence and clinical outcomes, we examine both PNA and SNA to chronic medications. The main strength of this study was the use of data from an integrated system, which provided the opportunity to accurately identify primary nonadherence and to control for many observable patient and prescriber characteristics, including lab values. Due to differences in baseline patient characteristics among adherence groups, it was imperative to control for differences to avoid biased results for health outcomes. However, there may still be some unobservable characteristics not captured in our data.

Limitations

A study limitation is the relatively short follow-up period for hospital and ED events due to limitations in data availability, which may explain why statistical significance could not be determined for this study outcome. Given

the short follow-up period, we were unable to evaluate other outcomes of interest such as cardiovascular events associated with hyperlipidemia. Such events were rare during the limited follow-up period in our study. Future studies should use longer follow-up periods that allow for adequate power when examining the association between PNA and cardiovascular outcomes.

In recent years, many health plans and provider groups have implemented policies to improve secondary medication adherence.[17] By contrast, PNA has been largely ignored. Our results suggest that new investments in health information technology will allow more providers and health plans to contact patients who do not fill or refill a prescription on a timely basis to discuss with them the reasons behind their decision, and allow them to intervene when applicable.

CONCLUSIONS

PNA and SNA were directly related to short-term clinical markers. This study provides evidence that clinical interventions should target both PNA and SNA in a timely fashion when EMR data are available. The results of this research advance the study of medication adherence and provide insight on the impact of both PNA and SNA on health, and how physicians can interpret clinical markers to assess patient behaviors.

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REFERENCES

1. Haynes RB, McKibbon KA, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *Lancet.* 1996;348(9024):383-386.

2. Evans CD, Eurich DT, Remillard AJ, Shevchuk YM, Blackburn D. First-fill medication discontinuations and nonadherence to antihypertensive therapy: an observational study. *Am J Hypertens.* 2012;25(2):195-203. doi: 10.1038/ajh.2011.198.

3. Liberman JN, Hutchins DS, Popiel RG, Patel MH, Jan SA, Berger JE. Determinants of primary nonadherence in asthma-controller and dyslipidemia pharmacotherapy. *Am J Pharm Benefits.* 2010;2(2):111-118.

4. Shin J, McCombs JS, Sanchez RJ, Udall M, Deminski MC, Cheetham TC. Primary nonadherence to medications in an integrated healthcare setting. *Am J Manag Care.* 2012;18(8):426-434.

5. Kazerooni R, Watanabe JH, Bounthavong M. Association between statin adherence and cholesterol level reduction from baseline in a veteran population. *Pharmacotherapy.* 2013;33(10):1044-1052. doi: 10.1002/phar.1305.

6. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care.* 2005;43(6):521-530.

7. Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med.* 2006;166(17):1842-1847.

8. Zhang Q, Safford M, Miller D, et al. Short-term statin exposure is associated with reduced all-cause mortality in persons with diabetes. *Med Care.* 2007;45(4):308-314.

9. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344(8934):1383-1389.

10. Sacks RM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med.* 1996;335(14):1001-1009.

11. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med.* 1998;339(19):1349-1357.

12. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360(9326):7-22.

13. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med.* 1995;333(20):1301-1307.

14. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA.* 1998;279(20):1615-1622.

15. Raebel MA, Ellis JL, Carroll NM, et al. Characteristics of patients with primary non-adherence to medications for hypertension, diabetes, and lipid disorders. *J Gen Intern Med.* 2012;27(1):57-64. doi: 10.1007/s11606-011-1829-z.

16. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889-2934. doi: 10.1016/j.jacc.2013.11.002.

17. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA.* 2002;288(22):2868-2879. Review. . ajpb