ORIGINAL RESEARCH

The Comparative Effectiveness of Mail Order Pharmacy Use vs. Local Pharmacy Use on LDL-C Control in New Statin Users

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BACKGROUND: Mail order pharmacies are commonly used to deliver CVD risk factor medications. Previous studies have shown that mail order pharmacy use is associated with greater medication adherence; however, no studies have examined whether mail order pharmacy use is related to improved CVD risk factor outcomes.

OBJECTIVE: To examine the comparative effectiveness of mail order pharmacy vs. local pharmacy use on LDL-C control in new statin users.

DESIGN: Observational cohort study.

PATIENTS: 100,298 adult Kaiser Permanente Northern California (KPNC) members who were new users of statins between January 1, 2005 and December 31, 2007.

MEASUREMENTS: The main outcome measure was LDL-C control in the 3–15 month period after statin therapy was initiated.

RESULTS: After adjustment for patient, clinical, and census-block characteristics, and for potential unmeasured differences between mail order and local KPNC pharmacy users with instrumental variables analysis, 85.0% of patients who used the mail order pharmacy to deliver their statin at any time achieved target LDL-C levels compared with 74.2% of patients who only used the local KPNC pharmacy to dispense the statin (p<0.001). Greater adjusted rates of LDL-C control in mail order pharmacy users were seen across all gender and race/ethnicity subgroups.

CONCLUSIONS: Mail order pharmacy use was positively associated with LDL-C control in new statin users. Future research should continue to explore the relationship between mail order pharmacy use and outcomes, and address how to appropriately target mail order services to patients most likely to benefit without compromising patient choice, care, and safety.

INTRODUCTION

Many Americans taking regular medications have the option of using either local pharmacies or mail order pharmacies to fill their prescriptions[1]. One report suggests that up to 1/3 of medications for chronic conditions are delivered via the mail[2], and a 2009 report suggests that mail order pharmacies account for almost 25% of pharmacy sales in the U.S.[3] While recent data suggests that the volume of prescriptions delivered via mail has stabilized and may be decreasing[3], others propose that the recent expansion of large retail outlets into the mail order pharmacy business means that mail order pharmacies may grow in the future[4]. The growth of mail order pharmacies to date has largely been driven by economic considerations, as some suggest that mail order pharmacy use may be cost-saving to health plans and to patients[5,6]. However, studies on whether mail order pharmacy use is actually cost-saving are mixed[7,8]. Studies also suggest that mail order pharmacy use may associated with greater patient satisfaction with prescription drug benefits and pharmacy services[9,10], although preference for mail order pharmacy over community pharmacies may be associated with different patient and benefit-level characteristics[11,12].

Despite extensive use of mail order pharmacies in the United States, there is almost no research examining the relationship between patients' mail order pharmacy use and clinical outcomes. A small number of recent studies have found a positive association between mail order pharmacy use and greater adherence to diabetes and antihypertensive medications[13–15]. In a prior analysis these authors found that compared to local pharmacy users, diabetes patients who primarily used mail order pharmacies had a 7–8 percentage point higher rate of good adherence to cardiometabolic therapies[15]. Greater adherence to these medications by mail order pharmacy users may reflect improved access to medications. Mail order does not require travel to the local pharmacy[15], which may be of particular benefit to patients with disabilities, time constraints, or limited access to transportation[15,16].

Previous studies have demonstrated that mail order pharmacy use is associated with greater levels of switching to generic medications[17]; this increased use of generic medications may reduce cost-related medication non-adherence in patients taking chronic medications. Greater adherence to cardiometabolic medications repeatedly has been shown to be associated with improved outcomes[18–20]; improved adherence to cardiometabolic therapies for mail order pharmacy users as compared with local pharmacy users may translate into improved intermediate outcomes, including better control of LDL-cholesterol (LDL-C) among statin users[21]. However, no study to date has directly examined the relationship between mail order pharmacy use and control of intermediate outcomes such as LDL-C. The purpose of this study is to examine the comparative effectiveness of mail order pharmacy vs. local Kaiser Permanente Northern California (KPNC) pharmacy use on achieving LDL-C control in a cohort of new users of statin medications, and to examine whether the effect of mail order pharmacy use varies by patient characteristics such as gender and race/ethnicity.

METHODS

Study Design/Participants

The study population consisted of KPNC members who were new users of statin medications between January 1, 2005 and December 31, 2007. Statin use was obtained from KPNC automated pharmacy records, which capture all prescriptions dispensed to members through a KPNC pharmacy. Patients were considered to be new users if they had no recorded use of a statin in KPNC records for 24 months prior to the initial statin prescription date (i.e. the "index" date). Patients were excluded from the analysis if they were <18 years of age by January 1, 2005, and did not have an active pharmacy benefit during the 2 years prior to the index date. We also excluded patients who did not refill the new statin medication at least once, since nearly all initial fills in the KPNC system are through the "brick and mortar" pharmacy. All subjects were required to have at least one LDL-C test result in the 12 months prior and the 3–15 months post the index date of the new statin prescription. New statin dispensings were captured and included if the statin was prescribed alone or as part of a combination drug with other medications used to treat dyslipidemia (e.g. ezetimibe/simvastatin).

Mail Order and Local Pharmacy Use within the KPNC System

KPNC maintains a mail order pharmacy distribution system in coordination with over 120 local "walk-in" KPNC pharmacies located within outpatient clinics and hospitals. KPNC patients have the option of filling both new and existing prescriptions either by mail or at one of the KPNC local pharmacies. KPNC members do have the option of filling prescriptions via non-KPNC local pharmacies; however, the cost of these fills would not be covered by the patient's pharmacy benefit. Mail order delivery of medications, with free shipping, can be requested either by phone or through the KP member website. Pharma-

cists are available via telephone to answer medication-related questions for members using either mail order or local KPNC pharmacies. There is no minimum or proscribed days' supply of pills required for mail order delivery, which typically dispenses 100-day medication supplies through both mail order and local KPNC pharmacies. Unlike some other mail order pharmacy systems, KPNC patients using the mail order pharmacy must request a prescription and provide up-front payment before the medication is delivered (i.e. no "auto-refills".) Some patients have a financial incentive to use mail order in the form of a lower co-payment for the same days' supply obtained by mail versus at a local KPNC pharmacy.

For the purposes of this analysis, patients were defined as local KPNC pharmacy users if they never used the mail order pharmacy to fill the new statin prescription in the 3–15 months post-statin initiation, and as a mail-order pharmacy user if they filled the new statin prescription at least once via the mail order pharmacy system during that timeframe.

Statistical Analysis

A potential concern in using observational studies to assess the effect of mail order pharmacy use on CVD intermediate outcomes is the potential for self-selection, or omitted (unmeasured) variable bias. For example, it is possible that patients who use mail order pharmacy services are intrinsically more motivated to take care of their health than patients who do not use such services; this characteristic cannot be directly measured in electronic databases. We provide two estimates of the comparative effectiveness of mail order pharmacy use vs. local KPNC pharmacy use on LDL-C levels; first, using a difference-in-differences approach[22,23], and then using the econometric technique of instrumental variables[15,24–27].

A probit model was used to examine the "difference in differences" in pre and post LDL-C control levels between mail order pharmacy and local KPNC pharmacy users, adjusting for patient, clinical, and census-block characteristics[22–24]. The last LDL-C value in the 12 months immediately prior to new statin dispensing was considered the "pre" value, and the last LDL-C value measured in the 3–15 month period after the first new statin dispensing was considered the "post" value. LDL-C levels in the first three months after dispensing were not examined in order to account for the gradual therapeutic onset of the new statin medication, and to also ensure that post-period LDL-C control was being assessed after mail order pharmacy use was initiated in the mail order group.

Depending on patient risk for adverse cardiovascular outcomes, two different thresholds for LDL targets were used[28]. Target LDL levels were set at LDL-C <100 mg/dL for patients with a "cardioequivalent" condition, including diabetes, stroke, or coronary artery disease. All other patients had an LDL-C target level of <130 mg/dL. The difference-in-differences models included dummy variables for time of LDL-C measurement (pre vs. post) and pharmacy type (mail order vs. local), as well as an interaction term between time of LDL-C measurement and pharmacy type. These analyses controlled for the effects of age, sex, race/ethnicity, presence of a cardioequivalent condition, number of comorbidities, smoking status, use of non-formulary medications, antidepressants, insurance type, whether the index medication was generic or brand

name, total days' supply, medical facility, follow-up time until the "post" LDL-C test, and number of primary care visits in the year prior to start of the statin medication. These variables were chosen because of their potential relationship with medication adherence, LDL-C levels, or both. Number of primary care visits was included in the model to adjust for potential differences in utilization and self-management practices between patients who use mail order pharmacy services vs. those who do not. Further information on these variables and their definitions is available elsewhere[15].

In the instrumental variables analysis, whether or not a patient had a financial incentive to order medications via the KPNC mail order pharmacy was used as the instrument under the assumption that having a financial incentive would affect the probability that a patient would use the mail order pharmacy (exposure), but should not directly affect whether a patient achieved LDL-C control (outcome). Analyses confirmed that having a financial incentive to use mail order was, in fact, associated with a greater likelihood of mail order pharmacy use in unadjusted and adjusted analyses (p<0.0001), but not independently or directly associated with LDL-C levels. We conducted tests for weak or irrelevant instruments and found none of these problems with our instrument[29] (see Appendix Table 3 for more details). The endogeneity test for omitted variable bias indicated that mail order use could not be considered exogenous (p=<0.001), meaning that the instrumental variables approach using bivariate probit analysis may provide a less-biased estimate of the effect of mail order pharmacy use on LDL-C control. Results from the difference-in-differences and IV analyses were very similar, and both are presented below. To facilitate interpretability of the results, adjusted regression results were converted to predicted percentages of patients reaching LDL-C target levels for both mail order pharmacy users and local KPNC pharmacy users overall and by key patient characteristics, holding all other covariates at their mean value.

All analyses were performed using Stata Version 10.1. The study protocol was approved by the KPNC Institutional Review Board.

RESULTS

A total of 100,298 new users of statin medications met study eligibility criteria. Of these, 29,279 (29.2%) used the mail order pharmacy at least once to refill their new statin medication during the study period (Table 1). Mail order pharmacy users were more likely to be white and to live in census tracts with higher socioeconomic status (p<0.001). Patients live, on average, less than 10 miles from the nearest KPNC local mail-in pharmacy regardless of whether they used mail order pharmacy services to deliver their medications. Mail order pharmacy users and local KPNC pharmacy users had identical LDL-C levels within both the 12-month period (130 mg/dL for both groups) and within the six-month period (147 mg/dL for both groups) prior to their start of a new statin medication. As demonstrated in previous studies[13–15], adherence of >=80% to the index statin medication, measured using the Continuous Medication Gaps (CMG) method[30–32], in the 15 months post-

statin initiation was higher in the mail order pharmacy group (87.8% vs. 72.9%, p<0.001).

Table 2 shows the results of both the difference-in-differences and instrumental variables multivariate models. In both models, mail order pharmacy use was positively and significantly associated with achieving LDL-C control in the 3–15 month period following the initiation of a new statin.

Figure 1 uses the results of the instrumental variables bivariate probit model to show the adjusted percents of patients considered in control of their LDL-C values based on their latest LDL-C lab value in the 3–15 months after initiation of the new statin medication. After adjustment for patient demographics, clinical characteristics, and census-block characteristics, 85.0% of patients who used the mail order pharmacy to deliver their statin medication at any time in the 3–15 month window achieved target LDL-C levels compared with 74.2% of patients who only used the local KPNC pharmacy to dispense the statin (p<0.001). The higher adjusted rates of LDL-C control in the mail order pharmacy vs. local KPNC pharmacy users were seen in both men and women, as well as in both white and non-white patients (p<0.01). African-American and Latino patients who used the mail order pharmacy also had higher adjusted LDL-C control rates compared to those who used the local KPNC pharmacy; however, these differences were not significant.

We performed a sensitivity analysis using only the patients with no financial incentive to use mail order. This was to address the issue of whether the financial incentive to use mail order, and the resulting potential out-of-pocket prescription drug cost difference between the mail order pharmacy and local KPNC pharmacy groups, might result in differential LDL-C outcomes. The results showed similar, statistically significant differences between LDL-C outcomes in mail order vs. local KPNC pharmacy users (data not shown).

DISCUSSION

This analysis is the first to examine the relationship between mail order pharmacy use and control of LDL cholesterol. This study found that despite equivalent LDL-C values at baseline, new statin users who primarily refilled by mail were more likely to be in control of their LDL-C levels within 3–15 months after medication initiation than patients who used local "brick-and-mortar" KPNC pharmacies. This positive association was consistent across patient gender and race/ethnicity. Consistent with previous studies, this study also found that use of mail order pharmacy was associated with better adherence to cardiometabolic medications[13–15]. Mail order pharmacy use may streamline the process of refilling medications, and improve access to medications by eliminating the need for travel to the pharmacy[15]. This improved access may be of particular importance to patients with inadequate transportation, disabilities, or time constraints[15,16]. Recent research suggests that mail order use may also improve medication adherence by promoting the use of less-expensive generic medications[17] and reducing refill complexity[33]. As demonstrated previously[21], this study suggests that this improved adherence may lead to the improved LDL-C outcomes among mail order pharmacy users seen in this analysis. While the findings of the present study should be

Table 1. Patient Characteristics by Pharmacy Type

	Entire Sample (n=100,298)	Local KPNC Pharmacy Use Only (n=71,019)	Mail Order PharmacyUse (n=29,279)
Demographics			
Female (%)	51.8	50.7	54*
Age (Mean)	61	61	63*
<40 (%)	3.9	4.4	2.6*
40-49 (%)	14.3	15.5	11.2*
50-59 (%)	28.4	28.8	27.3*
60-69 (%)	26.3	25.0	29.4*
70-79 (%)	19.1	18.5	20.5*
80+ (%)	8.1	7.7	9.0*
Race/ethnicity			
White, non-Latino (%)	51.7	45.3	67.2*
African American, non-Latino (%)	7.0	8.6	3.0*
Latino (%)	8.0	9.5	4.4*
Asian (%)	11.9	12.9	9.6*
Native American (%)	0.5	0.5	0.3*
Mixed-race (%)	3.7	4.1	2.8*
Missing race (%)	17.2	19.1	12.8*
Mean home to local pharmacy distance in miles (SD)	8 (16)	8 (16)	9 (18)*
Block Group Census Variables			
Mean Household Income ($)	$63,069	$61,363	$67,202*
Percent in Poverty (%)	7.6	8.1	6.5*
Percent with at Least a High School Education (%)	83.6	82.3	86.2*
Percent with at Least a Bachelor's Degree (%)	30.7	29.2	34.5*
Clinical Characteristics			
Mean LDL 12–6 months pre-statin (SD)	130 mg/dL (36)	130 mg/dL (36)	130 mg/dL (35)
Mean LDL 6–0 months pre-statin (SD)	147 mg/dL (39)	147 mg/dL (39)	147 mg/dL (38)
Mean number of comorbidities[1] (SD)	0.66 (0.88)	0.66 (0.88)	0.66 (0.89)
Has cardiovascular equivalents[2] (%)	38.3	39.7	34.6*
Using medication for depression (%)	21.9	20.9	24.4*
Using nonformulary medication (%)	5.5	5.4	5.7
New medication is brand-name (%)	3.5	3.3	4.1*
Mean Number of Primary Care Visits in Year Prior to Index Date	4.08 (4.52)	4.15 (4.62)	3.92 (4.27)*
Medication Days Supply of 1st Refill			
1-30 days (%)	5.6	5.8	4.9*
31-60 days (%)	3.0	3.0	2.8
61-90 days (%)	14.8	15.3	13.7*
>90 days (%)	76.7	75.9	78.6*
Total Medication Days Supply in the 15-Month Period Following the Index Date (Range=1,525)			
Mean (SD)	398 (140)	374 (145)	456 (104)*
Median	430	400	500
Total # of Refills in the 15-Month Period Following the Index Date (Range=19)			
Mean (SD)	3 (2)	3 (2)	4 (1)*
Median	4	3	4
Length of Follow-up, Index Date to Post-Period LDL Date (Range=363)			
Mean (SD)	319 (98)	313 (101)	334 (90)*
Median	339	332	353
Mean Statin Adherence in the 15 -Month Period Following the Index Date (SD)	77.2 (24.5)	72.9 (25.9)	87.8 (16.4)*
Mean Statin Adherence during Follow-up (SD)	80.6 (23.5)	76.7 (25.2)	90.0 (15.0)*
Insurance Characteristics			
Part D group coverage (%)	9.6	9.6	9.8
Part D individual coverage (%)	11.2	9.4	15.4*
Non-Medicare coverage (%)	79.2	81.1	74.8*
Financial incentive for mail-order use (%)	21.8	18.3	30.4*

*Difference between mail order and local pharmacy use is statistically significant (p-value<0.001)

[1]*Comorbidities counted are atrial fibrillation, osteoarthritis, depression, congestive heart failure, chronic obstructive pulmonary disease (COPD), renal failure/insufficiency, and smoking*

[2]*Dichotomous variable that equals one if patient has diabetes mellitus, coronary artery disease (CAD), or stroke; equals zero otherwise*

confirmed in a randomized controlled trial, they provide new evidence indicating that mail order pharmacy use may be associated with improved care and outcomes for patients with risk factors for CVD, and underscore the potential benefit of home delivery of medications directly to patients[16].

Mail order pharmacy services, which are provided at the health care delivery system level, rather than the physician or practice level, can be considered a structural or system-level intervention for improving access to chronic illness medications by making medications available to patients without the need to travel to a "brick-and-mortar" pharmacy[15]. Studies suggest system-level barriers to medication acquisition are usually not addressed when new medications are prescribed to patients[34,35]. System-level efforts to promote mail order use in patients that

Table 2. LDL-c Control (1=In control; 0=Not in Control)

	Probit (Difference-in-Differences Analysis)		Bivariate Probit (IV Analysis)	
Used mail order pharmacy to refill statin	0.4475***	(0.0173)	0.3865***	(0.0854)
Post period	1.9908***	(0.0126)	n/a	n/a
Length of follow-up	−0.0004***	(0.0000)	−0.0009***	(0.0000)
Total statin days supply	0.0024***	(0.0000)	0.0033***	(0.0000)
Gender: female	−0.3330***	(0.0094)	−0.1958***	(0.0096)
Age at statin initiation	0.0121***	(0.0004)	0.0092***	(0.0004)
African American	−0.0578**	(0.0195)	−0.0599**	(0.0193)
Asian	0.1241***	(0.0153)	0.1212***	(0.0160)
Latino	0.1121***	(0.0177)	0.0778***	(0.0180)
Native American	0.1858**	(0.0652)	0.1166	(0.0675)
Mixed Race	0.0865***	(0.0242)	0.0299	(0.0247)
Race Missing	−0.0520***	(0.0137)	−0.0438**	(0.0136)
Block Group Census				
Mean household income	0.0000	(0.0000)	0.0000	(0.0000)
Percent in poverty	0.0022*	(0.0010)	0.0016	(0.0010)
% with high school education	−0.0009	(0.0006)	−0.0010	(0.0007)
% with at least a Bachelor's degree	−0.0006	(0.0005)	0.0001	(0.0005)
Number of comorbidities	0.0625***	(0.0057)	0.0098	(0.0059)
Has cardiovascular equivalents	−0.0520	(0.0096)	−0.2014***	(0.0097)
Using medication for depression	−0.0289*	(0.0116)	−0.0465***	(0.0118)
Using non-formulary medication	−0.4048***	(0.0222)	−0.4524***	(0.0212)
Index statin is brand-name	0.3435***	(0.0271)	0.2496***	(0.0277)
# of primary care visits in prior year	0.0120***	(0.0011)	0.0076***	(0.0011)
Medicare Part D group coverage	0.1461***	(0.0166)	0.1580***	(0.0184)
Medicare Part D individual coverage	0.0816***	(0.0159)	0.0504*	(0.0206)
Constant	−2.5446***	(0.0714)	−0.8286***	(0.0753)
ρ (disturbance correlation)	n/a	n/a	−0.1568**	(0.0530)

Notes: (1) table shows estimated coefficients with standard errors in parentheses; (2) models control for patient's home medical facility (where KP walk-in pharmacy is located); (3) difference-in-differences analysis uses random effects on panel dataset where N=99,702 and T=2 (pre and post period)
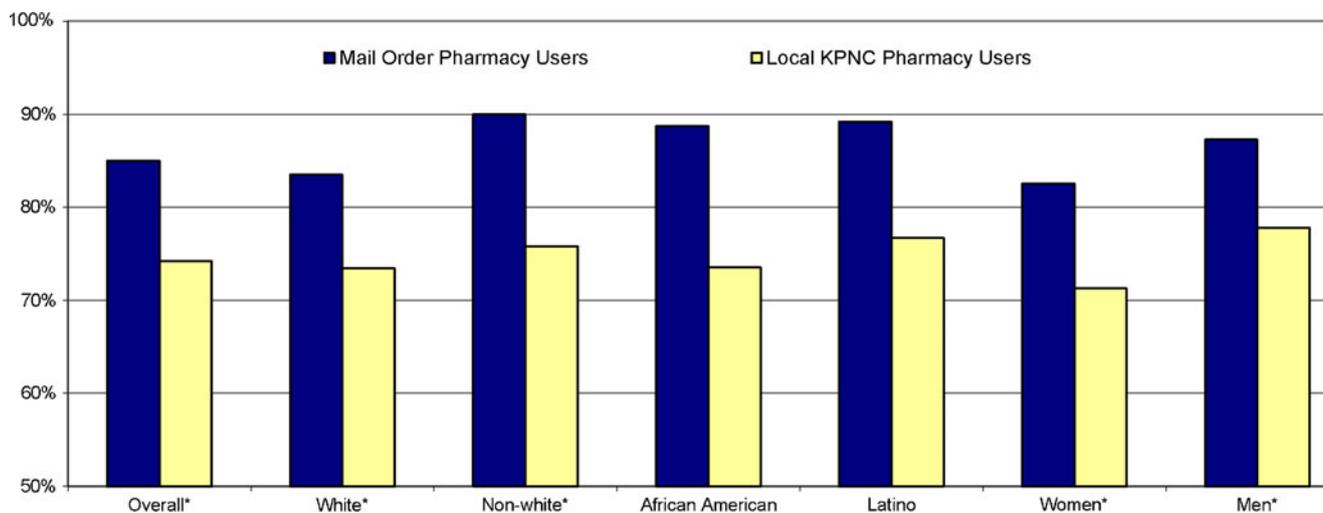*p-value<0.05
**p-value<0.01
***p-value<0.001

may benefit from its use, while preserving patient choice in what type of pharmacy services they prefer to use, have the potential to address medication access and adherence issues for new users of statin medications, and could lead to improved outcomes. This study found a similar positive association between mail order pharmacy use and LDL-C control in men and women, and in both minority and white patients, suggesting that such efforts to encourage mail order pharmacy use would provide benefits to patients regardless of gender and race/ethnicity. Since earlier studies of mail order pharmacy services suggest they are cost-

*p-value <0.01 for mail order vs. local KPNC pharmacy users

Figure 1. Adjusted percents of patients in LDL-C control 3–15 months after first statin fill.

saving to patients[3,4] and may be also cost-saving for health care delivery systems[3], increasing the proportion of prescriptions refilled by mail has the potential to be a cost-effective intervention for improving CVD risk factor control among diverse groups of patients at high risk for adverse outcomes.

Interventions to encourage the use of, and improve access to, mail order pharmacy use would need to be designed and targeted in a way that does not produce unintended consequences for patients. While the current study adds to the evidence suggesting that patients might benefit from increased mail order pharmacy use, the impact of mail delivery of medications on patient safety has not been studied. While KPNC's mail order pharmacy system provides telephone access to pharmacists, it is possible that providing medications through the mail reduces important face-to-face interactions with pharmacists and primary care providers; these interactions may help prevent multiple drug interactions and facilitate appropriate preventive care such as laboratory monitoring for patients on certain drug therapies[36]. Some patients may also be hesitant to use the mail order pharmacy because of unsecured mailboxes or other security reasons. Future research should address the important issue of how to appropriately target mail order pharmacy services without compromising care for patients that can benefit from the interactions that come along with in-person medication acquisition and consultation.

This study has several limitations that should be noted. First, observational studies such as this one cannot entirely control for differences between patients who utilize mail order pharmacy services and those that do not. While we utilized both difference-in-differences and instrumental variable analyses to minimize such biases, and both analyses showed a positive significant association between mail order pharmacy use and LDL-C control, it is possible that we were unable to completely control for these differences.

It is important to note that this study took place in an integrated delivery system where patients access their prescription medications differently than in many other settings. Patient experience with "brick and mortar" pharmacy for filling medications is primarily limited to the KPNC local pharmacy, and unlike in many settings KPNC's mail order pharmacy and local pharmacies do not differ in the standard amount of pills prescribed[15]. In addition, KPNC provides relatively easy access to mail order pharmacy services, without requiring physician sign-ups or changes in days' supply[15]. It is therefore possible that the use of mail order pharmacy services in KPNC has a different impact on intermediate outcomes than in other settings.

Finally, this study examined only the effects of new statin use on LDL-C outcomes, and did not examine the effects of mail order pharmacy use on outcomes for other CVD risk factors or for outcomes associated with chronic diseases such as asthma or depression. Future work should continue to explore the relationship between mail order pharmacy use and patient outcomes across other quality indicators.

CONCLUSION

Mail order pharmacy use is associated with improved LDL-C control in new statin users. System-level interventions to improve the rates of mail order pharmacy use may be an important strategy for improving processes and outcomes of care for patients with chronic illness, and potentially for addressing disparities in these outcomes among minority patients. This approach should be evaluated in randomized controlled trials testing the effectiveness of different methods of encouraging mail order use among patients on both increasing mail order pharmacy use and improving patient outcomes.

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APPENDIX

The results in Table 3 support our use of instrumental variables to estimate our model and in using financial incentive as the instrument for mail order pharmacy use.

Table 3. Instrumental Variables Tests[†]

Endogeneity test	23.97
	$p = < 0.001$
Test of excluded instruments (first-stage F-stat)	1573.27
	$p = < 0.001$
Weak-instrument-robust inference	42.46
	$p = < 0.001$
Overidentification test	Equation exactly identified
Underidentification test	1415.48
	$p = < 0.001$

[†]*Tests performed in linear model of LDL-c using ivreg2 command in Stata. See Baum, Schaffer, & Stillman (2007) for details of these tests*