By Alexis A. Krumme, Robert J. Glynn, Sebastian Schneeweiss, Joshua J. Gagne, J. Samantha Dougherty, Gregory Brill, and Niteesh K. Choudhry

DOI: 10.1377/hlthaff.2017.0881
HEALTH AFFAIRS 37,
NO. 1 (2018): 125–133
©2018 Project HOPE—
The People-to-People Health
Foundation, Inc.

Medication Synchronization Programs Improve Adherence To Cardiovascular Medications And Health Care Use

ABSTRACT Medication synchronization programs based in pharmacies simplify the refill process by enabling patients to pick up all of their medications on a single visit. This can be especially important for improving medication adherence in patients with complex chronic diseases. We evaluated the impact of two synchronization programs on adherence, cardiovascular events, and resource use among Medicare beneficiaries treated between 2011 and 2014 for two or more chronic conditions—at least one of which was hypertension, hyperlipidemia, or diabetes. Among nearly 23,000 patients matched by propensity score, the mean proportion of days covered (a measure of medication adherence) for the control group of patients without a synchronization program was 0.84 compared to 0.87 for synchronized patients—a gain of 3 percentage points. Adherence improvement in synchronized versus control patients was three times greater in patients with low baseline adherence, compared to those with higher baseline adherence. Rates of hospitalization and emergency department visits and rates of outpatient visits were 9 percent and 3 percent lower in the synchronized group compared to the control group, respectively, while cardiovascular event rates were similar. Synchronization programs were associated with improved adherence for patients with cardiovascular disease, especially those with low baseline adherence.

Alexis A. Krumme (akrumme@bwh.harvard.edu) is a research scientist in the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, in Boston, Massachusetts.

Robert J. Glynn is a professor of medicine at Harvard Medical School, in Boston, Massachusetts.

Sebastian Schneeweiss is a professor of medicine at Harvard Medical School, a professor in epidemiology at Harvard School of Public Health, and vice chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital.

Joshua J. Gagne is an associate professor of medicine at Harvard Medical School and a pharmacoepidemiologist in the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital.

J. Samantha Dougherty is senior director of policy and research at Pharmaceutical Research and Manufacturers of America (PhRMA), in Washington, D.C.

Gregory Brill is a statistical programmer in the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital.

Complex chronic disease regimens can pose many challenges for patients, including the need for many trips to the pharmacy to fill their prescriptions. This can be particularly burdensome for older adults who are managing several chronic illnesses and can lead to medication nonadherence. For example, patients with cardiovascular disease have been found to make an average of twenty pharmacy visits annually.[1] Ten percent of such patients make forty-four or more visits annually, and their adherence rates are 8 percent lower than those of patients with the least complex prescription regimens—an effect that can translate into meaningful differences in clinical outcomes.[1,2]

Programs offered by pharmacies to synchronize the filling of prescriptions aim to simplify the refill process by enabling patients to pick up all of their medications during a single visit.[3–5] Standard components of medication synchronization programs, such as refill reminders and regular pharmacist appointments, are designed to maintain synchronization and reinforce adherence behaviors over time.

In 2014 an estimated 355,000 patients were enrolled in medication synchronization programs in 3,334 chain and retail store pharmacies

Downloaded from HealthAffairs.org on October 24, 2020.
Copyright Project HOPE—The People-to-People Health Foundation, Inc.
For personal use only. All rights reserved. Reuse permissions at HealthAffairs.org.

Niteesh K. Choudhry is a professor of medicine at Harvard Medical School, an associate physician in the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, and executive director of the Center for Healthcare Delivery Sciences, Brigham and Women's Hospital.

throughout the United States.[6] As of 2017, we estimate the number of patients to be more than 3.5 million. While enrollment has increased dramatically, these programs' effectiveness has not been evaluated fully. In particular, while programs run by geographically localized community pharmacies and mail-order pharmacies appear to improve adherence, the programs' impact in retail chains—where the majority of patients fill their medications—remains unknown,[7–12] as does the impact of synchronization programs on clinical outcomes and resource use.

In this study we evaluated the impact of two regional pharmacy–based medication synchronization programs on adherence to cardiovascular medications, cardiovascular clinical outcomes, and health care resource use for fee-for-service Medicare beneficiaries with hypertension, hyperlipidemia, or diabetes—three of the five most prevalent conditions among Medicare enrollees.[13]

Study Data And Methods

MEDICATION SYNCHRONIZATION PROGRAMS Participating in this retrospective analysis of medication synchronization programs were two of the earliest chain-pharmacy adopters: Thrifty White Pharmacy, a midsize chain with approximately 100 locations in six Midwestern states that began its synchronization program in 2011; and Publix Super Markets, a large chain with approximately 1,100 stores in seven Southeastern states that began its program in 2013. Both programs used an appointment-based model of medication synchronization, in which appointment reminders and access to pharmacists are core components, in addition to the synchronization itself.[14] Monthly appointments with pharmacy staff members were offered to patients and recommended if there were any changes in their regimen. The programs were available at no cost to anyone wishing to enroll and included a suite of monthly reminders to reinforce adherence. The programs additionally offered ad hoc connections to other pharmacy-based services such as immunizations and medication therapy management. Because these programs were two of the earliest chain-pharmacy medication synchronization programs in the United States, it unlikely that any of the patients in our study would have had knowledge of, been offered enrollment in, or previously been enrolled in a competing program.[6]

Thrifty White Pharmacy's program enrolled people taking at least two medications to treat a chronic condition. Publix Super Markets' program enrolled people taking three or more chronic disease medications as well as Medicare beneficiaries taking a medication covered by Medicare adherence Star Ratings.[15] Enrolled patients and pharmacy staff members selected a future fill date of one medication to be the synchronization starting date. Typically, this "anchor" fill was chosen to minimize copayments for the partial dispensings of all other medications that must occur to align all fill dates with the anchor fill date. In both pharmacies' programs the majority of patients had their prescriptions fully synchronized within thirty days of enrollment.

STUDY POPULATION AND DATA SOURCE We included fee-for-service Medicare beneficiaries who enrolled in one of the two medication synchronization programs between July 2011 (the earliest period of enrollment in either program) and June 2014, which ensured a minimum of six months of follow-up, given the available data from the Centers for Medicare and Medicaid Services (CMS). Patients must have had a prescription fill for the treatment of at least one of three cardiovascular conditions—hypertension, diabetes, and hyperlipidemia—within 90 days of program enrollment at a retail pharmacy and 180 days of continuous eligibility for Parts A, B, and D before this prescription fill. (For a study design figure, see online appendix exhibit A1.)[16] We chose these conditions because they are some of the most prevalent conditions in the Medicare population and those targeted by Part D adherence quality measures. The index date was defined as the first fill for an eligible medication on or after the enrollment date. During the 180-day period preceding the index date, patients were required to have had either prescription fills for two of the three cardiovascular conditions, or at least one prescription fill for a cardiovascular condition and one for another chronic condition identified by CMS as part of core Medication Therapy Management.[17] (For a complete list of conditions and medications classes, see appendix exhibit A2.)[16]

Eligible control patients were those living in a state having at least one eligible synchronized patient and with a prescription fill for a cardiovascular medication between July 2011 and June 2014 occurring at a different pharmacy from that used by any synchronized patient. The index date was defined as the prescription fill date for this medication. Thus, the control population consisted of patients who could have enrolled in one of the programs during the study period, yet were unlikely to have been in fact offered enrollment and declined. Control patients had the same requirements as synchronized patients for continuous Medicare eligibility and prior medication use. Controls were eligible for cohort entry once in every six-month

Downloaded from HealthAffairs.org on October 24, 2020.
Copyright Project HOPE—The People-to-People Health Foundation, Inc.
For personal use only. All rights reserved. Reuse permissions at HealthAffairs.org.

The intervention had the largest effect on adherence among patients with lower baseline adherence.

period but were matched only once (further described below).

We used Medicare pharmacy and medical claims data for the period 2011–14 for patients enrolled in Medicare Parts A, B, and D. These data contain complete information about eligibility as well as paid claims for all procedures, physician encounters, hospitalizations, and filled prescriptions (including doses dispensed and amounts paid by Medicare and the patient) reimbursed by Medicare. Area-level data on socioeconomic status, race/ethnicity, and educational attainment were obtained by linking patients' ZIP code of residence with data for 2010 from the Census Bureau.

COVARIATES For all patients, we constructed covariates that could be associated with program enrollment and cardiovascular-related clinical and health care outcomes—notably clinical comorbidity profile, medication burden and use patterns, sociodemographic characteristics, prior resource use, and benefit and index pharmacy characteristics in the 180 days before the index fill. Clinical comorbidity was defined as the presence of individual chronic conditions, with a focus on cardiovascular comorbidity, and was additionally summarized using the combined comorbidity score.[18] Medication burden was defined as the number of cardiovascular conditions for which the patient was taking at least one medication (up to three), number of chronic disease medication classes (up to twenty-six), and adherence to cardiovascular medication classes and all chronic disease medication classes. The latter was measured as the mean proportion of days covered (PDC) across medication classes with at least one fill during the baseline period, beginning with the first fill in this period. The PDC is the ratio of the total number of days on which the patient had medications available (the numerator) and the total number of days in the measurement period. This widely used measure has been well studied in several therapeutic classes.[19]

Sociodemographic characteristics included patients' age, sex, and race and ZIP code–level education, race/ethnicity, and household income covariates. Resource use was assessed using the number of outpatient office visits, total days hospitalized, number of emergency department (ED) visits, and any intensive care unit stay during the baseline period. Medicare Part D benefit characteristics included eligibility for the Part D Low-Income Subsidy, the plan premium amount, and whether the plan was a Program of All-Inclusive Care for the Elderly plan. Finally, we measured "healthy adherer" characteristics, behaviors that have been shown to be positively associated with medication adherence: receipt of influenza vaccine, fecal occult blood test, mammogram or prostate-specific antigen screening, or colonoscopy screening.[20,21]

OUTCOMES The primary study outcome was monthly adherence to cardiovascular medications during days 31–360 after the index date, following a 30-day induction period before programs could begin working. Furthermore, as with all claims-based methods of adherence estimation, the proportion of adherent days was 1.00 for virtually all patients in the first 30-day interval after the index date. Patients were censored when no follow-up data were available, as a result of administrative censoring or loss of Medicare enrollment.

Patients were followed for as many cardiovascular medication classes as they filled during follow-up, with all medications within a class considered as interchangeable. A monthly PDC was calculated for each eligible medication class, which was used to calculate an overall mean monthly PDC for a patient as the average PDC for all cardiovascular medication classes in a given thirty-day interval. We additionally evaluated monthly optimal adherence, defined as a PDC of at least 0.80 for all medication classes that a patient was eligible for in a given month.

Secondary outcomes were the incidence of a major adverse cardiovascular event and monthly health care resource use. A *major adverse cardiovascular event*, determined using *International Classification of Diseases*, Ninth Revision (ICD-9), and *Current Procedural Terminology* (CPT) codes, was defined as a diagnosis of myocardial infarction, unstable angina, stroke, or congestive heart failure over twenty-four months[22,23] (further details are provided in appendix exhibit A3).[16] We also evaluated this outcome including revascularization, by adding percutaneous coronary intervention and coronary artery bypass graft procedures. Health care resource use was measured as the monthly number of inpatient hospitalization stays or ED visits and the number of physician office visits over eleven thirty-day intervals.

Downloaded from HealthAffairs.org on October 24, 2020.
Copyright Project HOPE—The People-to-People Health Foundation, Inc.
For personal use only. All rights reserved. Reuse permissions at HealthAffairs.org.

STATISTICAL ANALYSIS We used a logistic regression model that predicted the probability of enrollment in a medication synchronization program as a function of all baseline covariates (for a complete list of covariates, see appendix exhibit A4)[16] to construct propensity scores for synchronized and control patients, which were used to match synchronized patients to up to three controls. Propensity score construction and matching were conducted sequentially in each six-month interval. Once a control patient was matched, the patient could not be used as a control in future intervals—which is similar to the design of a prospective randomized trial. Adherence and resource use outcomes were evaluated using generalized estimating equations. Rates of major adverse cardiovascular events were evaluated with a Cox proportional hazards model. (For complete statistical methods, see appendix exhibit A5.)[16]

We performed several subgroup analyses, rematching patients for each subgroup: program region; baseline PDC tertile; number of unique (by generic name) medications filled during baseline; receipt of the Part D Low Income Subsidy at index; and primary versus secondary prevention, with *secondary prevention* defined as diagnosis of myocardial infarction, unstable angina, stroke, congestive heart failure, peripheral artery disease, bleed, diabetic or hypertensive nephropathy, or PCI procedure during baseline.

We conducted several sensitivity analyses. First, during the study period, Publix offered three commonly prescribed generic cardiovascular medications free of charge to patients and insurers. To account for the possibility that these prescription fills were inconsistently submitted as Medicare claims before 2014, we removed patients from the Southeastern US region who filled these medications at the index date. Second, for the resource use outcomes, we used a Poisson distribution. Third, we evaluated whether our results changed when the baseline period for prescription drug inclusion criteria and covariates was extended to 365 days before the index date. Finally, we conducted an exploratory analysis of the average individual change in the number of prescriptions filled per unique fill date, with positive changes in synchronized compared to control patients indicating greater fill synchronization.

LIMITATIONS Our study had several limitations. First, the generalizability of results could be limited by the possibility that early enrollees in the two synchronization programs may have been more health conscious than the general Medicare population. This possibility may be borne out by the fact that we were not able to find adequate matches among the control population for 16 percent of the synchronized patients. As synchronization programs expand, it will be important to reevaluate the impact they may have on adherence and cardiovascular outcomes, particularly within patient subgroups whose clinical outcomes our study was underpowered to evaluate.

Second, while we were able to adjust for a large number of potential clinical and behavioral factors associated with the decision to enroll in a medication synchronization program, including "healthy adherer" variables, such patient characteristics might not be completely explained in administrative claims data and could have led to selection bias exaggerating the effectiveness of the programs.

Third, as with any intervention implemented under real-world conditions, several factors may have influenced how the intervention was delivered during our study period—for example, changes to how patients were targeted for enrollment. Insofar as these changes were reflected in measured covariates, our propensity score constructed in different time periods would have controlled for any potentially confounding effects. Moreover, Medicare Star Ratings for adherence characteristics of Part D plans were rolled out during our study period. This may have improved adherence over time, as plans became more actively involved in adherence management. However, we would not expect this to be differential between synchronized and control patients.

Finally, maintenance of synchronization over time in the two pharmacy programs could not readily be evaluated in this study. Our exploratory analysis of the number of prescriptions filled per unique fill date reassuringly suggests that greater consolidation of fills occurred during follow-up. However, understanding the average duration of enrollment could inform the setting of important quality improvement priorities for these programs.

Study Results

STUDY POPULATION AND CHARACTERISTICS After we applied all cohort inclusion criteria, the final study population consisted of 7,744 synchronized and 200,047 eligible control patient-observations for 62,413 unique patients. (For cohort inclusion criteria, see appendix exhibit A6.)[16] Before matching, synchronized patients tended to be about four years older, on average, than control patients and more often were white (appendix exhibit A4).[16] Synchronized patients were less likely to receive the Part D Low-Income Subsidy and tended to be taking medications in more chronic disease classes. The prevalence of

Downloaded from HealthAffairs.org on October 24, 2020.
Copyright Project HOPE—The People-to-People Health Foundation, Inc.
For personal use only. All rights reserved. Reuse permissions at HealthAffairs.org.

individual clinical comorbidities was relatively balanced between groups, with the exception of diabetes (which occurred in 56 percent of the synchronized group versus 42 percent of the control group).

The final matched cohort consisted of 6,519 synchronized and 16,286 control patients. (For a comparison of matched and unmatched synchronized patients, see appendix exhibit A7.)[16] After matching, covariates were well balanced between groups (exhibit 1). Nearly half of both groups of patients were taking medications for two cardiovascular conditions, and both groups had a mean adherence of 0.85 to their cardiovascular medications. Because program enrollment grew over time, we observed right-censoring of patients at the end of the available data: 25 percent of the cohort was censored by nine months of follow-up, and 57 percent by twelve months (data not shown).

ADHERENCE Mean adherence declined over time in both groups, with the effect size between them remaining constant (exhibit 2 and appendix exhibit A8).[16] Monthly PDC during follow-up was 0.03 points higher in synchronized compared to matched control patients, and synchronized patients had 8 percent higher odds of being optimally adherent to all of their cardiovascular medications over time, compared to control patients (exhibit 3).

EXHIBIT 1

Baseline demographic and clinical characteristics of patients in a medication synchronization program in two pharmacy chains, and control patients

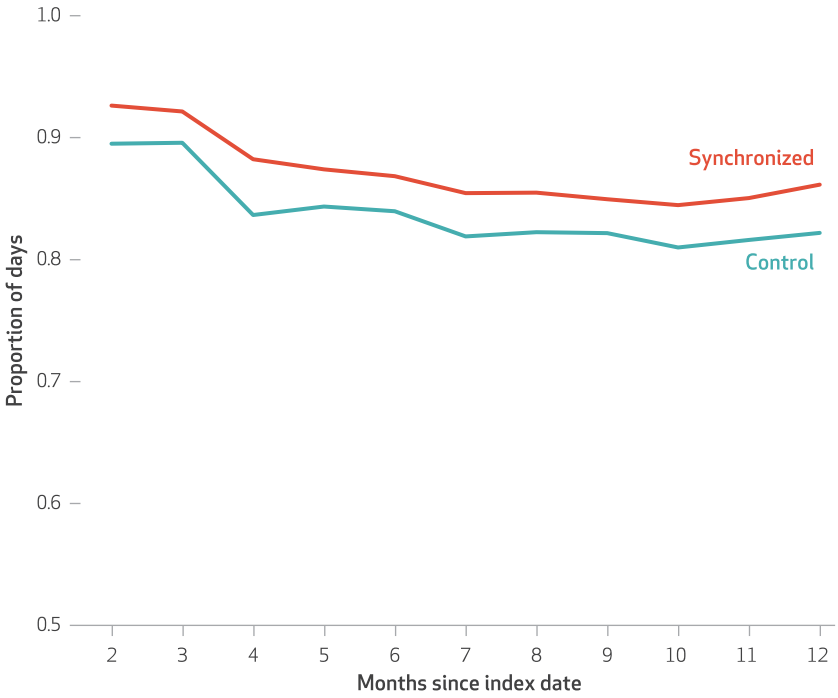
	Synchronized patients (*N* = 6,519)	Control patients (*N* = 16,286)	Absolute standardized difference[a]
Mean age (years)	74.0	74.3	0.03
Female (%)	60.8	61.2	0.01
Race (%)			
White	88.3	87.6	0.02
Black	3.8	4.2	0.02
Hispanic	5.3	5.9	0.02
Other or unknown	2.5	2.4	0.01
Participating program region (%)			
Southeastern (Publix)	54.6	54.6	0.00
Midwestern (Thrifty White)	45.4	45.4	0.00
Medicare benefits (%)			
Low-Income Subsidy in 3 of 6 months before index date	24.8	25.7	0.02
PACE plan	10.9	10.8	0.00
Chronic disease medication usage			
Mean number of chronic disease medication classes	5.1	5.1	0.00
Mean PDC, cardiovascular medication classes	0.85	0.85	0.01
Number of cardiovascular conditions (%)			
1	14.5	17.3	0.08
2	46.8	47.6	0.02
3	38.7	35.1	0.07
Clinical comorbidity (%)			
Hyperlipidemia	71.8	71.4	0.01
Hypertension	79.2	79.1	0.00
Diabetes	57.9	56.5	0.03
Heart failure	2.9	2.9	0.00
Asthma or COPD	21.3	21.5	0.01
Alzheimer or dementia	5.1	5.6	0.02
Depression	12.6	12.9	0.01
Cancer	9.2	9.2	0.00
Mean combined comorbidity score	1.2	1.2	0.02

SOURCE Authors' analysis of fee-for-service Medicare administrative claims data for 2010–14 and of Census Bureau data for 2010. **NOTES** Appendix exhibit A4 is a fuller version of this table, including data for the full cohort and a full list of covariates and standard deviations (see note 16 in text). The index date is the prescription fill date marking the beginning of follow-up. PACE is Program of All-Inclusive Care for the Elderly. PDC is proportion of days covered. COPD is chronic obstructive pulmonary disease. [a]Absolute value of the standardized differences of mean values between patients in a medication synchronization program ("synchronized") and those in the control group ("control").

Downloaded from HealthAffairs.org on October 24, 2020.
Copyright Project HOPE—The People-to-People Health Foundation, Inc.
For personal use only. All rights reserved. Reuse permissions at HealthAffairs.org.

EXHIBIT 2

Proportion of days covered by cardiovascular medications in months since the prescription fill index date



SOURCE Authors' analysis of fee-for-service Medicare administrative claims data for 2010–14. **NOTES** The index date is explained in the notes to exhibit 1. "Synchronized" refers to patients in a medication synchronization program. "Control" refers to patients in the control group. Numbers on the *x* axis begin at 2 months because follow-up for all outcomes began in the second month after the index date. In this exhibit, "months" equate to the 30-day intervals after the index date.

CARDIOVASCULAR AND HEALTH CARE OUTCOMES The event rate for major adverse cardiovascular events was 9.5 per 100 person-years in synchronized patients and 10.0 per 100 person-years in control patients (exhibit 3). Synchronized patients had nonsignificantly lower rates of major adverse cardiovascular events. Kaplan-Meier plots suggested an effect of the intervention beyond the first year of follow-up (appendix exhibit A9),[16] and a test of an interaction term between the exposure and time at one year of follow-up was significant ($p < 0.0001$). Subsequent stratification of the Cox proportional hazards models on follow-up time up to versus after one year suggested an effect after one year, although confidence intervals were overlapping (data not shown). Average monthly rates of hospitalization and ED visits and of outpatient visits were 9 percent and 3 percent lower, respectively, in the synchronized group compared to the control group.

SUBGROUP ANALYSES The proportion of patients achieving optimal adherence was higher in the Thrifty White program (11 percent versus 5 percent for the Publix program), though the mean difference in PDC between groups was the same in the two programs (exhibit 4). Patients with the lowest baseline adherence (PDC $\leq$ 0.70) had the largest gains in adherence associated with the intervention. The corresponding odds of optimal adherence were 19 percent higher in synchronized versus control patients with baseline PDC $\leq$ 0.70 and 7 percent higher in synchronized versus control patients with baseline PDC greater than 0.70 and up to 0.85. Receipt of the Part D Low-Income Subsidy was associated with small increases in optimal adherence.

SENSITIVITY ANALYSES Results were robust to sensitivity analyses. In particular, the extension of the prescription drug baseline period to 365 days yielded a matched cohort and results similar to those in the main analysis (93 percent of synchronized patients from the main analysis were included), as a result of the similarities in baseline period adherence and medication use characteristics (appendix exhibit A10).[16] In an exploratory analysis of the number of prescription fills per unique fill date, we found that synchronized

EXHIBIT 3

Adherence, major adverse cardiovascular event, and health care resource use outcomes for synchronized and control patients

Outcome and measure	Synchronized patients	Control patients	Point estimate from model: synchronized vs. control
Average monthly proportion of days covered	0.87	0.84	0.03[a] ****
Average proportion of patients optimally adherent	63.7%	57.6%	1.08[b] ****
Rate for major adverse cardiovascular event[c]	9.5	10.0	0.95[d]
Average monthly hospitalizations and ED visits	0.045	0.048	0.91[e] **
Average monthly physician office visits	0.77	0.80	0.97[e] **

SOURCE Authors' analysis of fee-for-service Medicare administrative claims data for 2010–14. **NOTE** ED is emergency department. [a]Difference between patients in a medication synchronization program ("synchronized") and those in the control group ("control"). [b]Odds ratio, synchronized to control. [c]Composite of myocardial infarction, unstable angina, stroke, and congestive heart failure, per 100 person-years. [d]Hazard ratio, synchronized to control. [e]Rate ratio, synchronized to control. **$p < 0.05$ ****$p < 0.001$

Downloaded from HealthAffairs.org on October 24, 2020.
Copyright Project HOPE—The People-to-People Health Foundation, Inc.
For personal use only. All rights reserved. Reuse permissions at HealthAffairs.org.

EXHIBIT 4

Adherence outcomes stratified by key baseline characteristics

	Synchronized patients	Control patients	Proportion synchronized matched[a]	Adherence outcomes: Difference in PDC	Adherence outcomes: Odds ratio, optimal adherence
Participating program region					
Midwest (Thrifty White)	2,958	7,390	0.75	0.03****	1.11****
Southeast (Publix)	3,561	8,896	0.94	0.03****	1.05****
Baseline adherence level					
PDC[a] ≤ 0.70	1,303	3,362	0.95	0.06****	1.19****
0.70 < PDC ≤ 0.85	1,975	4,982	0.92	0.02****	1.07****
PDC > 0.85	3,654	8,954	0.87	0.02****	1.04****
Number of unique medications (median: 9)					
At or above median	3,525	8,655	0.90	0.03****	1.08****
Below median	3,218	8,105	0.84	0.03****	1.08****
Part D Low-Income Subsidy (LIS) at index date					
No LIS	4,909	12,028	0.83	0.03****	1.08****
Full or partial dual LIS	1,610	4,092	0.88	0.04****	1.10****
Primary versus secondary prevention[b]					
Primary	5,463	13,587	0.85	0.03****	1.08****
Secondary or at high risk	1,205	2,973	0.90	0.03****	1.07***

SOURCE Authors' analysis of fee-for-service Medicare administrative claims data for 2010–14. **NOTES** The index date is explained in the notes to exhibit 1. PDC is proportion of days covered. [a]Proportion of synchronized patients matched to control patients. [b]Secondary prevention is defined as the presence of diagnosis code(s) for myocardial infarction, unstable angina, stroke, congestive heart failure, peripheral artery disease, bleed, diabetic or hypertensive nephropathy, or percutaneous coronary intervention procedure during the baseline period. Primary prevention is the absence of such a diagnosis. ***$p < 0.01$ ****$p < 0.001$

patients had a 23 percent increase in the number of fills per visit during follow-up, on average, compared to a 3 percent increase among control patients (appendix exhibit A11).[16]

Discussion

In this study of fee-for-service Medicare beneficiaries, enrollment in a medication synchronization program at Thrifty White Pharmacy or Publix Super Markets was associated with a small but significant improvement in adherence to cardiovascular medications and significant reductions in hospitalizations or ED visits and outpatient visits. Program enrollment was also associated with nonsignificant reductions in major adverse cardiovascular events—reductions that were larger in magnitude beginning twelve months after enrollment. The intervention had the largest effect on adherence among patients with lower baseline adherence.

Our results are similar to those from an evaluation of a mail-order refill synchronization program conducted in a population of Medicare managed care beneficiaries,[9] which suggests that addressing logistical issues related to medication supply may be the principal mechanism for these programs' success. That study was restricted to patients who received all of their medications by mail and whose prescriptions did not include medications with atypical refill schedules. In contrast, our study provides nationally representative results for patients in the manner in which most patients fill their medications and suggests that retail and mail-order populations may have similar responses to a medication synchronization intervention. While we were not able to determine which components of the pharmacy-based synchronization program were most effective, the moderate success of other pharmacist-led interventions to improve adherence may mean that further study of the long-term effects of engaging pharmacists in medication synchronization programs is warranted.[24]

Although significant, the magnitude of the adherence improvement from medication synchronization was modest. There are several potential explanations for this. First, our cohort was defined by patients who filled prescriptions for at least two chronic conditions in the baseline period. This requirement was implemented to form a cohort of patients who were "program eligible" per the programs' targeting criteria and the definition of *fill synchronization*, which requires the presence of more than one medication. Patients who were inconsistent fillers (that is, who had a

Downloaded from HealthAffairs.org on October 24, 2020.
Copyright Project HOPE—The People-to-People Health Foundation, Inc.
For personal use only. All rights reserved. Reuse permissions at HealthAffairs.org.

gap greater than six months between fills) or for whom the index was their first cardiovascular medication fill were excluded from our cohort. Consistent prevalent users are more likely to have an established routine for medication filling and may be less likely to benefit from the reminders and logistical support provided by such programs.[25] Moreover, before matching, synchronized patients exhibited high levels of baseline adherence, with mean PDC exceeding 0.84. High adherence at baseline could lead to a ceiling effect, whereby these patients may be able to achieve only small additional gains. Indeed, larger associations were observed in patients with lower baseline PDC.

Despite this, adherence improvements in our study were accompanied by small gains in health care resource use and nonsignificant reductions in major adverse cardiovascular event rates. These results are consistent with those of several studies of adherence-improving interventions that have found that even modest adherence differences of 4–6 percentage points translate into improved resource use and clinical outcomes over time.[2,26–28] Medication synchronization may lead to more consistent medication use, which allows patients to fully realize the benefits of prescribed therapy and averts health care encounters resulting from medication-related adverse events. Additionally, in medication synchronization programs, the pharmacist acts as an important patient resource and may help prevent unnecessary outpatient visits by addressing medication inconsistencies and possible medication errors, and by smoothing out prescription refills. The magnitude of improvement in health care resource use, while significant, was smaller than that observed following a copayment reduction intervention.[28] This suggests that addressing other barriers to adherence—such as medication costs—may more readily translate into clinical behavior change. Whereas improvement in major adverse cardiovascular events was observed, predominantly in the second year of follow-up, our study was underpowered to detect significant improvements in cardiovascular end points either in the first year or in subsequent time periods of interest. Significant right censoring of our cohort likely exacerbated this concern.

In subgroup analyses, we found that patients with the lowest tertile of baseline adherence had a threefold increase in effect size, compared to those in the other two tertiles. These results, which are aligned with findings from two other studies,[9,11] support the hypothesis that patients with erratic filling behaviors benefit more from the support provided by the program than do those with more consistent filling behaviors. Future programs may consider targeting outreach enrollment specifically to patients with lower adherence, who may benefit the most. Greater adherence gains among patients receiving the Part D Low-Income Subsidy, although small, suggest that removing cost barriers may work synergistically with a synchronization program. Interventions that reduce or eliminate copayments have been effective in improving adherence in other settings.[2,26] Exploring partnerships or opportunities to offer lower-price medications may be an effective way of improving enrollment and retention in medication synchronization programs. Policy-oriented changes, such as CMS's 2014 requirement that Part D plans offer prorated copayments for short fills, may also play an important role.[29]

Programs may consider targeting patients with lower adherence, who may benefit the most.

Few high-quality studies have been conducted to evaluate the impact of pharmacy-based medication synchronization programs on medication adherence and, more importantly, downstream health care outcomes.[6] This study demonstrates the potential of such programs to have a lasting impact on patient outcomes. Future research will need to evaluate the programs' benefit in other populations, the duration of effects, and whether benefits translate into cost savings for patients and insurers. ■

This work was supported by a grant from PhRMA to Brigham and Women's Hospital. At the time of the analysis, Alexis Krumme received tuition support from the Harvard T. H. Chan School of Public Health (partially supported by training grants from Pfizer, Takeda, Bayer, and Asisa).

Downloaded from HealthAffairs.org on October 24, 2020.
Copyright Project HOPE—The People-to-People Health Foundation, Inc.
For personal use only. All rights reserved. Reuse permissions at HealthAffairs.org.

NOTES

1 Choudhry NK, Fischer MA, Avorn J, Liberman JN, Schneeweiss S, Pakes J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. Arch Intern Med. 2011;171(9):814–22.

2 Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, et al. Full coverage for preventive medications after myocardial infarction. N Engl J Med. 2011;365(22):2088–97.

3 Ross A, Jami H, Young HA, Katz R. Sync and swim: the impact of medication consolidation on adherence in Medicaid patients. J Prim Care Community Health. 2013;4(4):240–4.

4 Agarwal S, Tang SSK, Rosenberg N, Pettitt D, McLaughlin T, Joyce A, et al. Does synchronizing initiation of therapy affect adherence to concomitant use of antihypertensive and lipid-lowering therapy? Am J Ther. 2009;16(2):119–26.

5 Delate T, Fairman KA, Carey SM, Motheral BR. Randomized controlled trial of a dose consolidation program. J Manag Care Pharm. 2004;10(5):396–403.

6 Krumme AA, Isaman DL, Stolpe SF, Dougherty S, Choudhry NK. Prevalence, effectiveness, and characteristics of pharmacy-based medication synchronization programs. Am J Manag Care. 2016;22(3):179–86.

7 Holdford DA, Inocencio TJ. Adherence and persistence associated with an appointment-based medication synchronization program. J Am Pharm Assoc (2003). 2013;53(6):576–83.

8 Patterson JA, Holdford DA, Saxena K. Cost-benefit of appointment-based medication synchronization in community pharmacies. Am J Manag Care. 2016;22(9):587–93.

9 Doshi JA, Lim R, Li P, Young PP, Lawnicki VF, State JJ, et al. A synchronized prescription refill program improved medication adherence. Health Aff (Millwood). 2016;35(8):1504–12.

10 Duru OK, Schmittdiel JA, Dyer WT, Parker MM, Uratsu CS, Chan J, et al. Mail-order pharmacy use and adherence to diabetes-related medications. Am J Manag Care. 2010;16(1):33–40.

11 Blackburn DF, Tran D, Quiring C. Evaluation of a refill synchronization program in two community pharmacies. J Am Pharm Assoc (2003). 2016;56(6):656–9.

12 DiDonato KL, Vetter KR, Liu Y, May JR, Hartwig DM. Examining the effect of a medication synchronization or an education program on health outcomes of hypertensive patients in a community pharmacy setting. Innovations in Pharmacy. 2014;5(3):article 175.

13 Centers for Medicare and Medicaid Services. Chronic conditions among Medicare beneficiaries, chartbook, 2012 edition [Internet]. Baltimore (MD): CMS; 2012 [cited 2017 Nov 15]. Available from: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/

14 American Pharmacists Association Foundation. Pharmacy's appointment based model: a prescription synchronization program that improves adherence [Internet]. Washington (DC): APhA Foundation; 2013 [cited 2017 Dec 7]. Available from: https://www.aphafoundation.org/sites/default/files/ckeditor/files/ABMImplementationGuide-FINAL-20130923.pdf

15 Centers for Medicare and Medicaid Services. Medicare 2016 Part C and D Star Rating technical notes: first plan preview: draft [Internet]. Baltimore (MD): CMS; [updated 2015 Aug 5; cited 2017 Nov 22]. Available from: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/Downloads/2016-Technical-Notes-Preview-1-v2015_08_05.pdf

16 To access the appendix, click on the Details tab of the article online.

17 Centers for Medicare and Medicaid Services. 2012 Medicare Part D Medication Therapy Management (MTM) programs [Internet]. Baltimore (MD): CMS; 2012 Nov 12 [cited 2017 Nov 22]. (Fact Sheet). Available from: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/CY2012-MTM-Fact-Sheet.pdf

18 Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. J Clin Epidemiol. 2011;64(7):749–59.

19 Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. An empirical basis for standardizing adherence measures derived from administrative claims data among diabetic patients. Med Care. 2008;46(11):1125–33.

20 Dormuth CR, Patrick AR, Shrank WH, Wright JM, Glynn RJ, Sutherland J, et al. Statin adherence and risk of accidents: a cautionary tale. Circulation. 2009;119(15):2051–7.

21 Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. Am J Epidemiol. 2007;166(3):348–54.

22 Cannon CP, Sharis PJ, Schweiger MJ, McCabe CH, Diver DJ, Shah PK, et al. Prospective validation of a composite end point in thrombolytic trials of acute myocardial infarction (TIMI 4 and 5). Thrombosis In Myocardial Infarction. Am J Cardiol. 1997;80(6):696–9.

23 Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359(9311):995–1003.

24 Cutrona SL, Choudhry NK, Fischer MA, Servi A, Liberman JN, Brennan TA, et al. Modes of delivery for interventions to improve cardiovascular medication adherence. Am J Manag Care. 2010;16(12):929–42.

25 Krumme AA, Franklin JM, Isaman DL, Matlin OS, Tong AY, Spettell CM, et al. Predicting 1-year statin adherence among prevalent users: a retrospective cohort study. J Manag Care Spec Pharm. 2017;23(4):494–502.

26 Hsu J, Price M, Huang J, Brand R, Fung V, Hui R, et al. Unintended consequences of caps on Medicare drug benefits. N Engl J Med. 2006;354(22):2349–59.

27 Gagne JJ, Choudhry NK, Kesselheim AS, Polinski JM, Hutchins D, Matlin OS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. Ann Intern Med. 2014;161(6):400–7.

28 Choudhry NK, Fischer MA, Avorn JL, Lee JL, Schneeweiss S, Solomon DH, et al. The impact of reducing cardiovascular medication copayments on health spending and resource utilization. J Am Coll Cardiol. 2012;60(18):1817–24.

29 Centers for Medicare and Medicaid Services. Advance notice of methodological changes for calendar year (CY) 2014 for Medicare Advantage (MA) capitation rates, Part C and Part D payment policies and 2014 call letter [Internet]. Baltimore (MD): CMS; 2013 Feb 15 [cited 2017 Nov 22]. Available from: https://www.cms.gov/medicare/health-plans/medicareadvtgspecratestats/downloads/advance2014.pdf

Downloaded from HealthAffairs.org on October 24, 2020.
Copyright Project HOPE—The People-to-People Health Foundation, Inc.
For personal use only. All rights reserved. Reuse permissions at HealthAffairs.org.