RESEARCH

Adherence to Statins in Primary Prevention: Yearly Adherence Changes and Outcomes

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ABSTRACT

BACKGROUND: Adherence to statins in real-world practice settings is known to be suboptimal. However, less is known about how adherence changes over time and whether changes in adherence are associated with adverse cardiovascular (CV) outcomes.

OBJECTIVES: To (a) characterize yearly changes in adherence among initially adherent patients taking statins for primary prevention and (b) assess the association between changes in statin adherence with subsequent risk of CV events.

METHODS: A 10% random sample of the IMS LifeLink Health Plan Claims Database covering the time period from July 1, 1997, to December 31, 2008, was used to identify a cohort of primary prevention statin users. Adherence was estimated in yearly segments beginning with the index statin prescription using proportion of days covered (PDC). PDC was categorized into 3 levels: PDC ≥ 0.80, 0.20 ≤ PDC < 0.80, PDC < 0.20. Patients were excluded if they experienced CV events or had PDC < 0.80 in their first year of statin exposure. Descriptive statistics were used to explore proportions of the cohort in each PDC category during each year. Cox-proportional hazards models were used to estimate the 5-year CV event risk associated with yearly adherence transitions.

RESULTS: Of the 11,126 patients beginning at the highest level of adherence (PDC ≥ 0.80) in year 1, 70% remained at this level in year 2. Of those in this level during year 2, 73% remained at this level in year 3. 828 (7.44%) experienced a CV event during their observable follow-up time. It was found that those who transitioned from the highest to the lowest level of adherence in year 2 (PDC < 0.20) experienced 2.26 greater CV event hazard ($P < 0.0001$). Adjusting for year 2 adherence, patients at the lowest level in year 3 experienced a 271% increase in CV hazard ($P < 0.0001$), as compared with the highest level of adherence.

CONCLUSION: This study found that patients' adherence levels tend to decline over time, and a transition to levels of adherence lower than a PDC of 80% was associated with increased risk of CV events. These results are useful in the context of targeting interventions that aim to improve patients' adherence.

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What is already known about this subject

- Literature exists on adherence to statins in the real world and its consequence.
- Statin adherence is known to be suboptimal in real-world practice.
- Few studies have investigated the effect of the observed nonadherence on cardiovascular (CV) outcomes specifically in primary prevention.
- Studies rarely examine adherence past the first year of statin use.

What this study adds

- This study characterized yearly statin adherence in primary prevention statin users in the United States.
- We examined statin adherence in 1-year periods over the 3 years following statin initiations.
- We associated yearly statin adherence transitions with the risk of CV events up to 5 years following statin initiation.

HMG-CoA reductase inhibitors (statins) are recommended as the first-line of drug therapy to meet low-density lipoprotein (LDL) cholesterol goals when lifestyle modifications are not effective and are therefore used ubiquitously in primary prevention of cardiovascular disease (CVD). Adherence to medications for the prevention of asymptomatic chronic diseases in real-world practice settings is known to be suboptimal.[1] Such is the case for statins used for hypercholesterolemia. This results in a challenge to treat patients, as statin benefits in routine clinical practice often do not mirror those seen in randomized controlled trials (RCTs).[2]

Literature exists on adherence to statins in the real world and associated consequences.[3-7] Fewer studies have investigated the effect of observed nonadherence on cardiovascular (CV) outcomes specifically in primary prevention.[8-11] Studies of Canadian statin users found an association between decreased adherence and increased risk of CV events.[8-11] A less-explored topic of interest is the description of adherence changes over time and how these changes are related to outcomes. Existing evidence in this area is sparse. It would be useful to examine adherence changes over time and the association with cardiovascular outcomes in a primary prevention cohort representative of U.S. managed care enrollees.

Our study contributes to the statin adherence literature by pursuing objectives seldom addressed in prior studies. The first objective of this study was to characterize yearly statin adherence transitions over time using pharmacy claims for a sample representative of primary prevention statin users in the United States who are initially adherent. The second objective was to associate yearly statin adherence transitions with the risk of CV events in the same sample. Using the selected cohort, we examined patients' statin adherence trends over time as well as their association with CV outcomes.

Methods

Data and Study Cohort

A 10% random sample of the IMS LifeLink Health Plan Claims Database covering the time period from July 1, 1997, to December 31, 2008, was used to identify a cohort of new primary prevention statin users. The LifeLink database contains paid claims data from managed care plans throughout the United States. The database includes medical and pharmacy claims from over 98 U.S. health plans, resulting in over 61 million unique patients. The majority of patient claims in the database are paid by a private commercial plan, but Medicaid, Medicare, and self-insured patients are also represented. Available data include demographic characteristics such as patient's year of birth and gender; dates of service; *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes; and prescription fill information such as drug code and days supplied.

Cohort Selection. We identified all patients with at least 1 statin prescription fill. The first occurrence of a statin prescription fill for each person was identified as the index statin fill on the index statin date. The cohort was restricted to patients who had at least 12 months of continuous enrollment prior to the index statin with no statin prescriptions during this time and at least 24 months of continuous health plan enrollment following the index statin. We used the lack of prior statin use during the 12-month window before the index statin prescription to define the individual as a new statin user. Continuous enrollment in the health plan was identified by consecutive health plan enrollment with no gaps greater than 1 month. Given these requirements, 24 months to approximately 10 years of follow-up was possible.

Statin prescriptions were identified using the first 2 characters of the 14-character generic product indicator (GPI) code for prescription drug claims. The drug classes used for statin identification were antihyperlipidemics (GPI code beginning 39) and cardiovascular agents (GPI code beginning 40). Within these broad classes, the first 6 characters of the GPI code were used to identify statins: 394000, 394099, 399940, and 409925. All medical and pharmacy claims associated with each new statin user were identified using unique patient identifier codes.

A number of exclusion criteria were applied to the study cohort definition (Figure 1). Criteria were developed to identify patients who were likely to be primary prevention statin users. Patients were excluded if they had at least 1 claim with a diagnosis (up to 4 diagnoses per claim) indicating cardiovascular disease during the 12 months preceding their index statin (n = 14,501; Figure 1). Cardiovascular disease was identified using ICD-9-CM codes 410.xx-411.xx (acute coronary syndrome), 413.xx (angina pectoris), 428.xx-429.xx (heart failure), 430.xx-438.xx (stroke), and 440.xx-448.xx (diseases of the arteries). Patients were also excluded if they met any of the following criteria: combination-agent statin prescriptions for the index statin (n = 2,835), as this may indicate nonprimary prevention statin use; any statin prescription claims with negative or missing days supplied (n = 2,058), or multiple statin fills on a single day (n = 2,944) to avoid imputation or double-counting of prescriptions in adherence calculation. Finally, patients who did not exhibit high adherence (defined below; n = 16,323) in their first year of statin use were excluded.

We were interested in assessing how changes in adherence affect outcomes in a cohort of statin users who are initially adherent. Restricting the analysis to a group with similar initial adherence also allowed us to isolate the effects of maintaining good adherence versus changing adherence over time. We also focused our analysis on statin users who initially exhibited high adherence in an effort to create a homogeneous population in the analysis. A commonly cited limitation in pharmacy claims studies is the inability to adjust for disease severity.[12]

FIGURE 1 Study Cohort Inclusion and Exclusion Criteria

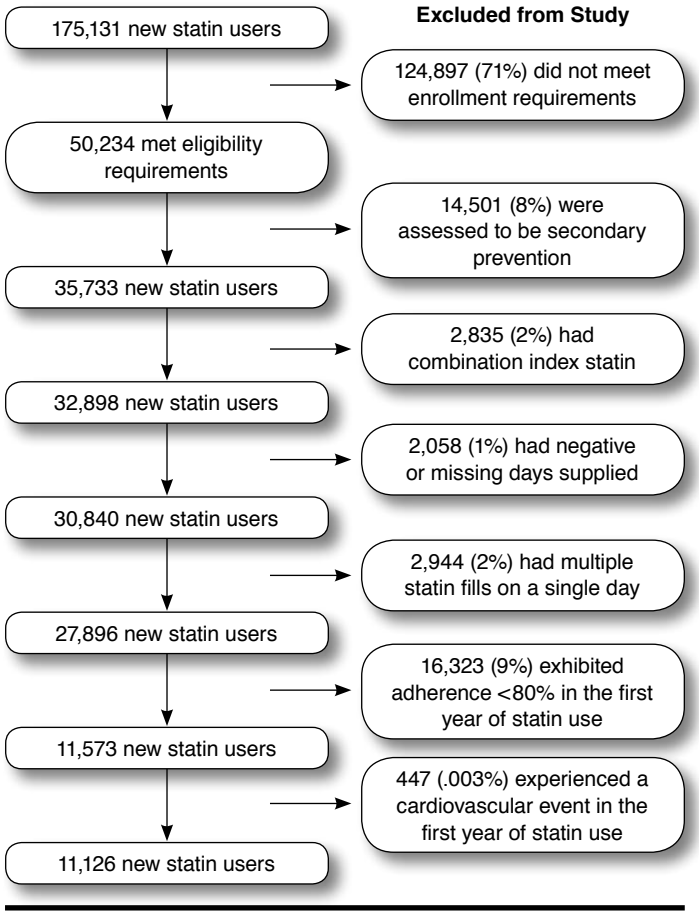

TABLE 1 Characteristics of the Study Population

Patient Characteristic	Total	Year 2 Adherence Level				
		PDC ≥ 0.80 (Reference)	0.20 ≤ PDC < 0.80	*P* Value (Reference = PDC ≥ 0.80)	PDC < 0.20	*P* Value (Reference = PDC ≥ 0.80)
	N = 11,126	n = 7,813	n = 2,673		n = 676	
Male, n (%)	5,581 (50.16)	3,985 (51.00)	1,304 (49.45)	0.167	292 (43.20)	< 0.001
Mean, age (SD)	55.85 (10.31)	56.30 (10.05)	54.72 (10.68)	< 0.001	55.09 (11.38)	0.004
Over 65 years, n (%)	1,951 (17.54)	1,422 (18.20)	407 (15.43)	0.001	122 (18.05)	0.921
Payer type, n (%)				< 0.001		0.008
Medicare	574 (5.16)	378 (4.84)	144 (5.46)		52 (7.69)	
Medicaid	38 (0.34)	27 (0.35)	9 (0.34)		2 (0.30)	
Commercial	9,448 (84.92)	6,586 (84.30)	2,300 (87.22)		562 (83.14)	
Other	1,066 (9.58)	822 (10.52)	184 (6.98)		60 (8.88)	
Geographic region n (%)				< 0.001		< 0.001
Northeast	2,196 (19.74)	1,498 (19.17)	561 (21.27)		137 (20.27)	
South	1,368 (12.30)	879 (11.25)	377 (14.30)		112 (16.57)	
Midwest	6,687 (60.10)	4,846 (62.02)	1,467 (55.63)		374 (55.33)	
West	875 7.86	590 (7.55)	232 (8.80)		53 (7.84)	
Prescribing physician, n (%)				0.141		0.004
General/family practitioner	3,500 (31.46)	2,500 (32.00)	797 (30.22)		203 (30.03)	
Internist	2,553 (22.95)	1,779 (22.77)	646 (24.50)		128 (18.93)	
Cardiologist	546 (4.91)	364 (4.66)	135 (5.12)		47 (6.95)	
Other type of physician/unknown	4,527 (40.69)	3,170 (40.57)	1,059 (40.16)		298 (44.08)	
Diabetes history n (%)	2,330 (20.94)	1,642 (21.02)	552 (20.93)	0.928	136 (20.12)	0.582
Hypertension history n (%)	5,252 (47.20)	3,761 (48.14)	1,195 (45.32)	0.012	296 (43.79)	0.030
Mean Chronic Disease Indicator score (SD)	4.85 (2.89)	4.85 (2.86)	4.84 (2.95)	0.407	4.94 (3.01)	0.417

PDC = proportion of days covered; SD = standard deviation.

Heterogeneity in initial statin adherence may indicate varying disease severity, potentially introducing unmeasured confounding into our analysis of CV events.

Those who experienced CV events in their first year of statin use (n = 447) were also excluded because it was likely that CV risk was not associated with such a short statin exposure time frame. The resulting cohort included 11,126 new primary prevention statin users (Figure 1). This research was exempt from review by the Colorado Multiple Institutional Review Board (Protocol 12-0391).

Measures

Prescription Fills and Statin Adherence. The data elements captured for both the index statin and subsequent prescription fills included the days supplied, GPI code and national drug code (NDC), and the strength and unit of the dose (e.g., 20 milligrams [mg]). The adherence analysis followed established definitions and guidelines for adherence studies.[13,14] Adherence was estimated in yearly segments beginning with the index statin prescription. All statin prescriptions were counted toward the yearly supply of statin, regardless of whether the patient switched statin type. Days supplied for statin fills were summed during 1-year periods (360 days, or less if a CV event occurred or enrollment ended) beginning with the index statin for up to 3 years of statin use. The yearly proportion of days covered (PDC) was calculated by dividing the summed statin days supplied by number of days in the yearly time period. In each period, surplus statin from overlapping refills were carried forward and/or carried over to the following period thereby reducing inflated adherence measures due to refills at the very end of the yearly period. Similarly, the days supplied in the final refill of the period were carried forward to the next period in proportion to the days left in the period. This method of carrying over refills is similar to that of previous studies.[15] A concern with measuring adherence over short periods is that outcomes are associated with a very short time frame of adherence (< 1 month) and may bias results. To approximate the magnitude of this issue in our study, we estimated that approximately 4% of the cohort had < 1 month for adherence estimation during either year 1 or year 2.

Because the interest of this study was patterns of statin exposure in primary prevention, adherence was estimated until the point of an identified CV event or the end of 3 years. PDC was categorized into 3 levels similar to previous studies: PDC ≥ 0.80, 0.20 ≤ PDC < 0.80, PDC < .20.[6,16] Adherence category (level) was assigned for each year, thereby allowing examination of the transition between levels in years 2 and 3.

TABLE 2 Patient Adherence Transitions, Years 1-3

Year 1 Adherence PDC ≥ 0.80 N = 11,126	Year 3 Adherence n = 10,771[a]		
Year 2 Adherence PDC < 0.20	**PDC < 0.20 n = 2,303**	**0.20 ≤ PDC < 0.80 n = 2,152**	**PDC ≥ 0.80 n = 6,316**
n = 676	n = 487	n = 73	n = 49
6.08%	79.97%	11.99%	8.05%
0.20 ≤ PDC < 0.80			
n = 2,673	n = 958	n = 882	n = 734
23.70%	37.22%	34.27%	28.52%
PDC ≥ 0.80			
n = 7,813	n = 858	n = 1,197	n = 5,533
70.22%	11.31%	15.77%	72.92%

[a]*Sample size decreased after year 2 due to noncontinuous health plan enrollment.*
PDC = proportion of days covered.

Cardiovascular Events. CV-event outcomes were identified in the cohort using all claims up to 5 years following the index statin (or until the patient had a gap in health plan enrollment). As previously described, diagnosis codes (up to 4 per claim) were used to identify the following CV events: myocardial infarction (MI; ICD-9-CM 410.xx), stroke (ICD-9-CM 430.xx-438.xx), and heart failure (ICD-9-CM 428.xx).

Patient Characteristics. A number of patient characteristics were captured at the time of the index statin fill and used as covariates. These characteristics were as follows: greater than 65 years of age (yes/no); male gender (yes/no); health plan payer type (Medicare, Medicaid, commercial, other); medical specialty of the statin prescriber (family practitioner, internist, cardiologist, other/unknown); and geographic region (Northeast, South, Midwest, West). The index statin was also classified as being high potency using the GPI (yes/no: atorvastatin or rosuvastatin vs. all other statins: fluvastatin, lovastatin, pravastatin, and simvastatin). The Chronic Disease Indicator (CDI), a score that indicates the total number of chronic diseases for a given patient using prescription claims, was estimated as a measure of comorbidity.[17] Claims prior to the index statin were also used to identify pre-existing diabetes (ICD-9-CM 250.xx) and hypertension (ICD-9-CM 401.xx-404.xx).

Analysis

Study population characteristics between year 2 adherence level groups were compared using chi-squared tests of proportions and Student's t-tests of means. The proportion of the cohort in each PDC category was calculated during each year. This method was also used to describe transitions in adherence level from year 2 to year 3.

The number and proportion of patients who experienced CV events were estimated during the patient's continuous enrollment period, up to 5 years. As previously noted, patients who experienced events in the first year of statin use were excluded from the analysis. Characteristics were described for those who did and did not experience events during the follow-up period. The characteristics explored were age, gender, statin type, geographic region, payer type, physician type, CDI, diabetes history, and hypertension history. Chi-squared tests of proportions and Student's t-tests were used to compare these measures between those who did and did not have CV events.

Cox-proportional hazards models were used to estimate the 5-year CV event risk associated with yearly adherence transitions. These multivariable models were adjusted for these independent variables: age (≥ 65 years, reference ≤ 65 years); male gender; geographic region (South, West, or Midwest, with Northeast as the reference category); payer (Medicare, Medicaid, or other type with commercial health plan as the reference group); and CDI score. Yearly adherence predictors were added in a stepwise approach. Models included either 1 lag (year 2 adherence level) or 2 lags (years 2 and 3 adherence levels entered as separate covariates) as predictors of CV event hazard.

Results

Patient Characteristics and Adherence Patterns

The cohort of 11,126 statin users was predominantly composed of patients with commercial health care plans (85%). The cohort was 50% male, and the mean age at statin initiation was 55.9 years. At statin initiation, 2,330 (21%) had a history of diabetes, and 5,252 (47%) had a history of hypertension, based on the medical claims available for the 12 months prior to the index statin date (Table 1).

The proportion of patients transitioning to each level of adherence over years 2 through 3 is described in Table 2. Patients tended to remain at their previous levels or transition to a lower level of adherence. All patients began at the highest level of adherence (PDC ≥ 0.80) in year 1; 70% remained at this level in year 2. Of those in this level during year 2, 73% remained at this level in year 3 (Table 2).

Patient characteristics were associated with the 3-level adherence measure in year 2 (Table 1). Prevalence of hypertension was 48% in those at the highest level of adherence in year 2, while 44% of those at the lowest adherence level in year 2 had hypertension ($P = 0.008$). There were larger proportions of those 65 years and older in the highest and lowest adherence categories as compared with the middle adherence category (18% vs. 15%, $P = 0.005$).

Cardiovascular Outcomes

CV Events and Associated Characteristics. In the 11,126-person cohort, 828 (7.44%) experienced a CV event during their observable follow-up time. The mean follow-up time was 42 months for all patients (range 24-119 months). The mean time to CV event was 3.3 years. While the proportion of the cohort greater than aged 65 years was small overall, a higher proportion of those who had events were in this age group (42% vs. 16%,

TABLE 3 5-Year CV Event Hazard and Year 2 Adherence Level

Year 2 Adherence Definition N = 11,126	Hazard Ratio	*P* Value	95% CI
PDC ≥ 0.80	reference		
PDC < 0.20	2.257	< 0.001	(1.801, 2.828)
0.20 ≤ PDC < 0.80	1.079	0.366	(0.915, 1.273)

CI = confidence interval; CV = cardiovascular; PDC = proportion of days covered.

TABLE 4 5-Year CV Event Hazard and Year 3 Adherence Level

Year 3 Adherence Definition N = 10,771	Hazard Ratio	*P* Value	95% CI
PDC ≥ 0.80	reference		
PDC < 0.20	2.714	< 0.001	(2.089, 3.527)
0.20 ≤ PDC < 0.80	1.160	0.230	(0.910, 1.480)

CI = confidence interval; CV = cardiovascular; PDC = proportion of days covered.

$P < 0.001$). Those who had CV events had significantly greater CDI scores (6.9 vs. 4.7, $P < 0.001$). The prevalence of pre-existing diabetes was significantly greater in those who had events (26% vs. 21%, $P < 0.001$) as was pre-existing hypertension (52% vs. 47%, $P = 0.004$).

Survival Model Results. The second-year adherence level was found to be a significant predictor of CV event hazard ($P < 0.001$). Those who transitioned to the lowest level of adherence (PDC < 0.20) in year 2 experienced 2.26 greater CV event hazard compared with those who remained at the highest level ($P < 0.001$; Table 3). There was no significant difference in the event hazard between those who remained at the highest level and those who transitioned into the middle level ($P = 0.366$). Year 3 adherence level was also found to be a significant predicator, while adjusting for the year 2 level ($P < 0.001$). Patients at the lowest level in year 3 experienced a 271% increase in event hazard ($P < 0.001$), as compared with those with the highest level of adherence (Table 4).

Discussion

Our study has contributed to the literature on statin adherence and outcomes by addressing topics seldom explored in past studies. Erstwhile, the oft-cited 80% threshold for good adherence[6,7,18] was used ubiquitously in adherence studies. Recently, it has been suggested that adherence studies using pharmacy claims data consider measures of adherence based on nondichotomous thresholds.[19] Furthermore, there is a dearth of literature that describes adherence transitions over time and the association of adherence changes with CV outcomes, especially in U.S. patient populations. Studies typically focus on characterizing nonadherence in 1 period and its effect on outcomes. Two Perreault et al. (2009) studies described the association of adherence quintiles with CV outcomes in a Canadian study population but did not focus the analysis on the transitions of patients among levels.[10,11] Studies that have focused on adherence transitions over time have not described their associations with CV outcomes directly.[16,20] We have addressed the gap in this literature by using a nondichotomous adherence measure to examine adherence transitions over the 3 years following statin initiation. We have also measured the association between these transitions and outcomes.

Among our initial cohort of new primary prevention statin users, 41% of patients were in the highest category (PDC ≥ 0.80) during year 1 (these patients were ultimately excluded from our analyses). Using this upper limit cutoff allowed comparability with other studies of yearly statin adherence. Two other studies explored such adherence-level transitions. Nichol et al. (2009) determined adherence rates and transition probabilities in antihypertensive and lipid-lowering medications simultaneously.[16] They found that only approximately 21% of patients exhibited a PDC ≥ 0.80 to lipid-lowering medications in their first year of use. It is difficult to directly compare these findings wirh ours, however, because this population was concurrently using antihypertensives. Our cohort likely had a lesser degree of concomitant hypertensive medication use. Mason et al. (2012) studied yearly adherence to statins in a group of diabetes patients and found that 49% of patients exhibited high adherence (PDC > 0.80) in their first year of statin use, similar to what was found in this study.[20]

Our first study objective was to describe adherence levels and transitions. Among our cohort of patients who began at the highest level of statin adherence (PDC ≥ 0.80), 70% remained at this level, while 30% transitioned to a lower level. Mason et al. found similar results: 74% of patients remained at the highest level.[20] We found that 73% of patients exhibiting high adherence in year 2 remained at this level in year 3. In total, 59% of patients exhibited this level of adherence in year 3. Furthermore, by stratifying adherence of PDC < 0.80 into 2 categories (PDC < 0.20 and 0.20 ≤ PDC < 0.80), statin users' behavior became more apparent. We found that of those patients whose adherence dropped to a lower level in year 2, 6% exhibited adherence of PDC < 0.20; by year 3, this proportion had increased to 21%. A benefit to a 3-level categorization is that multiple levels of adherence may be associated with changes in outcomes as well.

The second study objective was to estimate risk of CV events up to 5 years following statin initiation associated with transitions among levels of adherence over time. Among our cohort of highly adherent patients in their first year of statin use, 828 patients (7.44%) experienced a CV event in the years following statin treatment (up to 4 years of follow-up). As compared with those remaining in the highest level of adherence, those transitioning to the lowest level had 126% increased

hazard. Similar results were found associating adherence transitions from year 2 to year 3. These findings may be compared with those of several other studies. Perreault et al. explored the odds of stroke associated with quintiles of statin adherence.[11] At adherence ≥80%, a 26% risk reduction was seen, as compared with adherence <20%. Intermediate levels were associated with risk reductions of 3%-18%. This is similar to the trend and significant association found in our study. Rublee et al. (2012) found that atorvastatin users who were adherent had an 18% reduction in CV risk as compared with those who were nonadherent.[21] Mason et al. estimated changes in cholesterol associated with levels of adherence, which were then linked to CV event probability.[20] While these results are not directly comparable with this study, it was found that the percentage of decrease in total cholesterol was reduced for patients whose adherence was 40%-80% and further in those with lower adherence, as compared with those with adherence >80%.[20] Cherry et al. (2009) examined adherence transitions and their association with potential changes in outcomes but assumed an interpolation between zero and full effectiveness.[22]

While characterizing statin exposure over a single time period is useful, it poses difficulties in characterizing gaps and changes in adherence. By characterizing adherence changes over time in shorter time periods (1 year), we were able to better characterize patients whose statin adherence increased or decreased. Furthermore, these patterns may be associated with changes in outcomes. Examining adherence changes over time identified different behaviors than would be identified by estimating an average adherence over patients' entire statin-using lifetime. For example, the scenario in which a patient may not use statins at all for 1 or more years, and then continue statin use, would be apparent by assessing adherence transitions. These changes in adherence over time are important in characterizing patients' behavior but also in estimating the effect of statin exposure on outcomes. The adherence transitions we found are notable because in many adherence analyses they are obscured by using an overall, multiyear adherence analytic approach. Our findings are therefore an addition to the existing statin adherence literature.

Limitations

A number of limitations should be considered alongside the results of this study. First, several issues typical to pharmacy claims data analysis are present here. A major assumption with all claims-based adherence studies is that patients who fill their prescriptions are actually taking the medication. Relatedly, the exact use of the filled prescription is not clear. Some patients may receive instruction from their physicians to split tablets, for example. This pattern may or may not be discernible in claims data. Similarly, we cannot observe whether patients begin using $4 generics and therefore appear to be nonadherent. Four dollar generic fills would not be tracked in claims data. This analysis did not consider whether the type of statin changed after the index fill.

The analysis considered whether patients refilled any type of statin, regardless of dose or whether it had changed from the index statin type. Future work may characterize switches. In this analysis, statin potency was only measured in the initial statin fill. A limitation of this simple characterization is that statin users may switch to another, often higher potency, statin, which may be associated with different adherence behaviors and outcomes. This would be an important area for future study. Finally, this analysis did not adjust for differential cost-sharing or a healthy-adherer effect, which likely influences adherence level.[23] Future work may include this as a covariate in adherence modeling.

The study population included first-time statin users who did not have any CV diagnoses or statin use during the 12 months prior to their index statin fill. The population was also limited to those patients who had at least 24 months of follow-up claims information. These criteria allowed the assumption that this sample was representative of patients who were taking statins for the purposes of primary prevention. This study only considered medication use up until a CV event. Patients' adherence and persistence behavior may change following a CV event, a time period not considered by the current study. Relatedly, patients with events occurring at the beginning of a period have observed adherence over a short time frame in that period. Such cases may bias results associating the level of adherence in that short time frame with the outcome experienced. We estimated that only 4% of our cohort had a short time frame for observation. Future work may consider using a method that captures changing adherence as a time-dependent covariate over shorter time periods for outcomes assessment to address this methodological concern.

Conclusions

To the authors' knowledge, this is the first study that describes statin adherence transitions over yearly time periods and describes the effect of these transitions on CV outcomes in a U.S. primary prevention population. While many studies have examined adherence patterns, especially in statin use, few have attempted to link these patterns to outcomes in the longer term. This study found that patients' adherence tends to decay over time and a transition to levels of adherence lower than a PDC of 80% was associated with increased risk of CV events.

This study fills a major gap in the current knowledge of statin adherence. New evidence has been added to the existing literature associating CV outcomes with adherence transitions. Recent attention has been given to interventions that aim to improve patients' adherence.[24] Understanding how patients' adherence may change after beginning statin use at a high level of adherence may help direct these efforts.

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DISCLOSURES

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