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ORIGINAL REPORT

Association between trajectories of statin adherence and subsequent cardiovascular events

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ABSTRACT

Purpose Trajectory models have been shown to (1) identify groups of patients with similar patterns of medication filling behavior and (2) summarize the trajectory, the average adherence in each group over time. However, the association between adherence trajectories and clinical outcomes remains unclear. This study investigated the association between 12-month statin trajectories and subsequent cardiovascular events.
Methods We identified patients with insurance coverage from a large national insurer who initiated a statin during January 1, 2007 to December 31, 2010. We assessed medication adherence during the 360 days following initiation and grouped patients based on the proportion of days covered (PDC) and trajectory models. We then measured cardiovascular events during the year after adherence assessment. Cox proportional hazards models were used to evaluate the association between adherence measures and cardiovascular outcomes; strength of association was quantified by the hazard ratio, the increase in model C-statistic, and the net reclassification index (NRI).
Results Among 519 842 statin initiators, 8777 (1.7%) had a cardiovascular event during follow-up. More consistent medication use was associated with a lower likelihood of clinical events, whether adherence was measured through trajectory groups or PDC. When evaluating the prediction of future cardiovascular events by including a measure of adherence in the model, the best model reclassification was observed when adherence was measured using three or four trajectory groups (NRI = 0.189; 95% confidence interval: [0.171, 0.210]).
Conclusions Statin adherence trajectory predicted future cardiovascular events better than measures categorizing PDC. Thus, adherence trajectories may be useful for targeting adherence interventions. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—adherence; comparative effectiveness; epidemiologic methods; prediction; trajectories

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BACKGROUND

Suboptimal adherence to prescribed medications has been shown to result in higher rates of adverse events, worse long-term outcomes, and higher healthcare costs.[1,2] However, adherence remains low, with nearly 50% of patients becoming nonadherent within a year of treatment initiation.[3–5] In order to design targeted interventions to improve adherence, methods are needed that can accurately predict patients' adherence behaviors by identifying if and when nonadherence are likely to occur.[6] Thus, predictions should be targeted to measures of adherence that capture both the duration and intensity of medication taking.[7]

In administrative claims data, adherence measurement and classification have most often been accomplished with measures of medication possession, such as the proportion of days covered (PDC) with medication during follow-up, the medication possession ratio, or the continuous measure of medication gaps.[8,9] Among these, PDC and its closely related measures are the most widely used; they have been well studied in several therapeutic classes,[10,11] and a relationship between statin PDC in particular and clinical outcomes has been established.[12] However, this measure reduces adherence behaviors during the entire period of follow-up to a single number. Patients with very different adherence patterns may have the same PDC value, thereby missing distinctions among unique patient behaviors that can have important implications for intervention effectiveness and patient prognosis.

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Group-based trajectory modeling offers an alternative approach in which individuals are grouped according to their prescription filling patterns over time.[13,14] This method has been shown to summarize longitudinal adherence better than conventional approaches,[13] and it provides an easily understandable graphical depiction of medication use in each group. Despite these benefits, it is unclear whether adherence trajectories are associated with clinical outcomes of interest. Therefore, the objective of this study was to evaluate the association between statin adherence trajectories measured over the year following statin initiation and subsequent cardiovascular events.

METHODS

Data source and cohort

We used data from the UnitedHealth Optum Research Datamart from January 1, 2006 to December 31, 2011, which includes data on patients with commercial insurance plans through UnitedHealth, as well as patients with a Medicare supplement plan. The database contains deidentified claims for billable medical services that record both inpatient and outpatient diagnoses and procedures along with pharmacy and mail-order prescription dispensings that enable the description of medication initiation and refill patterns.

We identified patients enrolled in UnitedHealth who initiated a statin during January 1, 2007 to December 31, 2010. Initiation was defined as a patient's first statin fill with continuous enrollment in UnitedHealth and no statin use during the 365 days prior. Patients were followed for medication use beginning on the day of initiation (the index date) and were required to have at least 360 days of available follow-up in order to ensure complete assessment of medication use during this period. Any additional follow-up beyond this period, up to a maximum of 725 days, was used for assessment of cardiovascular outcomes (Web Figure 1). In order to limit the scope of the population under study as well as the size of the study sample, we excluded patients if they received any prescriptions by mail during the medication assessment period, if they had a statin combination drug as their index statin fill, or if they were not between the ages of 35 and 64 on the index date.

The institutional review board of Brigham and Women's Hospital approved this study.

Adherence measures

For each patient in the cohort, we created a "supply diary" indicating whether medication was available on each day during the 360 days of adherence assessment. This diary linked all observed statin fills based on the dispensing date and the days' supply. Fills from overlapping supplies were accumulated up to a maximum excess of 180 days of medication. From the supply diary, we calculated the PDC over the entire 360-day assessment period.

We also calculated PDC separately during each of the 12 consecutive 30-day periods of adherence assessment and created a binary indicator for "full adherence" each month, defined as PDC $\geq$ 0.8 (or $\geq$ 24 days covered, equivalently). This PDC value corresponds to the level of use above which patients with coronary artery disease are known to benefit from statins[12] and the threshold employed by most quality measures.[15,16]

We then modeled the 12 binary indicators of full adherence during each 30-day period as a longitudinal response in a logistic group-based trajectory model.[17,18] In a trajectory model, several regression models are estimated simultaneously, including a multinomial logistic model that estimates the probability of membership in each group, as well as logistic models that estimate the probability of being adherent over time as a smooth function of time. We estimated our model using between two and six adherence groups, as in prior research,[13] assessing each through comparison of the Bayesian Information Criterion, as recommended in the literature.[19] In each group, we used a third-order polynomial (linear, squared, and cubic terms) of time to model the probability of being adherent, except in the two-group model where unstable model convergence required using second order polynomials. On the basis of these models, we assigned patients to a trajectory group, which created five different groupings of patients (one grouping resulting from the two-group model, one grouping resulting from the three-group model, etc.). We implemented models with "PROC TRAJ", a free downloadable add-on package to base SAS (SAS, version 9.3; SAS Institute Inc., Cary, NC, USA). This estimation procedure has been shown to be superior for identifying underlying longitudinal trajectories.[20]

Outcome

After the adherence assessment period, beginning at 361 days after statin initiation, patients were followed for a combined cardiovascular outcome, defined as the first hospitalization for an acute coronary event, revascularization, a cerebrovascular event, or heart failure. Outcome algorithms, defined using ICD-9 codes, are given in Web Table 1. Time until event was recorded as days since the end of the adherence assessment period. Patients were followed until the first

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event during follow-up, end of enrollment or data availability, or death, and patients were not excluded if the outcome occurred during the adherence assessment period. Follow-up for outcomes was restricted to the first 365 days after the adherence assessment period, in order to ensure that we were only capturing clinical events that were proximal to the measurement of medication use.

Covariates

We evaluated potential confounders of the association between statin adherence and cardiovascular events using enrollment files and medical and pharmacy claims incurred during the 365 days before statin initiation. These variables included demographic information, such as age and sex, and features of the index statin prescription, including days supply (>30 versus ≤ 30), type of statin, and dose (high-intensity versus low-intensity; see Web Table 2). Clinical characteristics included number of distinct drugs and a prior diagnosis of acute coronary syndrome, chronic coronary disease, revascularization, atrial fibrillation, congestive heart failure, hyperlipidemia, hypertension, peripheral vascular disease, stroke, and diabetes mellitus. Finally, variables intended to indicate patients' health seeking behavior were assessed, including receipt of an influenza vaccine, a pneumonia vaccine, colon cancer screening, and gender-specific screening (mammography for women and prostate-specific antigen testing for men).

Statistical analysis

We used Cox proportional hazards models to evaluate the association between statin adherence and cardiovascular events. In each model, the dependent variable was time until first cardiovascular event. In the base model, the independent variables included all covariates listed above. In 11 subsequent models, we evaluated the effect of adding one adherence measure to the base model. For example, in a second model, we added an indicator for the adherence trajectory to which each patient belonged, based on a two-group trajectory model. In a third model, we included all covariates and indicators for trajectory grouping from the three-group model. Models that included four, five, and six trajectory groups were also considered.

To compare adherence trajectory groupings with PDC, we created similar groupings based on quantiles of PDC. To create two and three groups from PDC, we categorized patients by median and tertile of PDC, respectively. Similarly, PDC groupings with four, five, and six groups were created. We additionally considered a binary PDC grouping based on a threshold of 80% of days covered. As with the trajectory groupings, each potential grouping was included with other covariates in a model for time until cardiovascular event.

The association between each adherence group and outcome was evaluated based on its estimated hazard ratio (HR). In addition, the cumulative association between an adherence grouping and cardiovascular events was measured through increases in the C-statistic when adding that adherence grouping to the base model with no adherence information. The C-statistic measures the ability of a model to discriminate between patients who did and did not have an event, and it ranges from 0.5 to 1.0, corresponding to a completely noninformative model and perfect prediction, respectively.[21] If a given adherence grouping has a strong independent association with the outcome, then adding this information to the model would be expected to increase the C-statistic.

Similarly, we calculated the continuous net reclassification improvement (NRI) of each model over the base model, which measures the net proportions of cases and controls that are correctly reclassified by the expanded model that includes adherence information.[22] A patient is considered to be correctly reclassified if the predicted probability of outcome for that patient moves in the correct direction when adding adherence information to the model, that is, an increase in predicted probability for a case or a decrease for a noncase. Findings from NRI calculations complement those from C-statistics, because NRI can capture subtle changes in model predictions that may be missed by the C-statistic.[23] As recommended in the literature, both the C-statistic and NRI for a survival endpoint were calculated with bootstrapped 95% confidence intervals.[24,25] All analyses were performed in SAS version 9.3.

RESULTS

Cohort characteristics

Our cohort consisted of 519 842 statin initiators, including 8777 patients (1.7%) that experienced a cardiovascular event during the outcome follow-up period. Patients who experienced an event were generally older, more likely to be male, to have a higher medication count, and to have nearly all assessed comorbidities than patients who did not have an event (Table 1). All differences were statistically significant ($p < 0.001$).

Adherence trajectory groups are presented in Figure 1. In each plot, the trajectory with the most consistent filling patterns was labeled as trajectory group 1, with

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Table 1. Patient characteristics of statin initiators in UnitedHealth, 2006–2010, separately by event status

Characteristics	Cardiovascular events $n = 8777$	No observed event $n = 511\,065$
Follow-up time; mean (SD)	154 (106)	307 (102)
PDC; mean (SD)	0.52 (0.32)	0.54 (0.32)
Age		
35–40	4.27	9.47
41–46	11.35	16.92
47–52	21.77	25.00
53–58	30.65	27.13
59–65	31.96	21.48
Female gender	35.78	45.36
Index statin fill		
Days supply ≥ 30	7.14	8.78
Generic	54.95	60.51
High dose	37.10	28.40
GPI8 count		
2-Jan	6.84	14.91
5-Mar	20.57	31.47
9-Jun	26.88	29.26
10+	45.72	24.35
Acute coronary syndrome	20.15	4.15
Chronic coronary disease	43.50	11.79
Revascularization	14.97	2.90
Atrial fibrillation	3.62	0.69
Congestive heart failure	14.07	2.05
Disorders of lipid metabolism	79.30	80.57
Hypertension	74.90	54.57
Peripheral vascular disease	1.88	0.24
Stroke	5.42	1.43
Diabetes mellitus	43.73	25.06
Kidney disease	8.31	1.89
Flu vaccine	15.44	14.68
Pneumonia vaccine	3.05	2.03
Gender-specific screening	36.36	44.57
Colon cancer screening	3.74	3.85

All values are in per cent unless otherwise indicated.

increasing group number corresponding to generally declining overall adherence. In the six-group model, 21.1% of the cohort had perfect or near-perfect adherence across the 12 months of adherence assessment (group 1), while 19.5% were almost entirely nonadherent, primarily comprised of patients who filled an initial 30-day prescription and then did not fill again for the remainder of adherence follow-up (group 6). The remaining 59.4% of patients were moderate adherers, including group 2, which was defined by a "brief gap" in medication use, group 3 by a "slow decline" in adherence, group 4 by only "occasional use", and group 5 by "rapid decline" in use after initiation. Baseline characteristics by trajectory group in the six-trajectory model are shown in Web Table 3.

The mean PDC within each adherence group was similar whether groups were based on trajectory models or quantiles of PDC (Table 2).

Association between adherence and risk of cardiovascular events

As shown in Table 1, patients who had a cardiovascular event had a lower mean PDC, although this measure differed only slightly between the two groups of patients. Similarly, in Table 2, patients who had an event were more likely to be in lower adherence groups, whether those groups were based on trajectory models or PDC.

Figure 2 displays the HRs for the associations between adherence grouping and the combined cardiovascular outcome. In all models, the group with the lowest level of adherence was the reference. For adherence groups based on either PDC or trajectories, better adherence corresponded to lower risk of cardiovascular hospitalizations. For example, with three trajectory groups, moderate adherence (trajectory 2) was associated with an 18% reduction in risk (HR: 0.82, 95% confidence interval: [0.78, 0.86]), while the best adherence group (trajectory 1) was associated with a 36% reduction in risk (HR: 0.64, 0.60–0.67). An exception to this finding occurred with five trajectory groups, where patients in trajectory 3 had lower rates of events than patients in trajectory 2, despite that trajectory's better overall adherence.

When PDC was categorized based on the usual cutpoint of 80% adherence, results were similar to splitting at the median (HR: 0.73, 0.70–0.76).

Prediction of cardiovascular events from adherence groupings

Table 3 displays C-statistics, indicating the predictive accuracy of each potential model and NRI comparing each model that includes adherence information to the base model. The case NRI and control NRI indicate the proportion of cases and controls, respectively, that were correctly reclassified, minus the proportion that were incorrectly reclassified; a negative value indicates that more patients were reclassified incorrectly than correctly. The overall NRI combines the data from both cases and controls.

Cardiovascular events were predicted well from the base model that did not include any assessment of adherence with a C-statistic of 0.771 (95% confidence interval: [0.751, 0.789]). Adding an indicator of good adherence increased the C-statistic slightly, whether adherence was classified by PDC or by group-based trajectory models. Increasing the number of groups used to describe adherence had little impact on the C-statistic.

When improvement in discrimination was assessed using NRI, adding adherence groupings to the base model improved prediction of cardiovascular events, and the amount of improvement varied depending on

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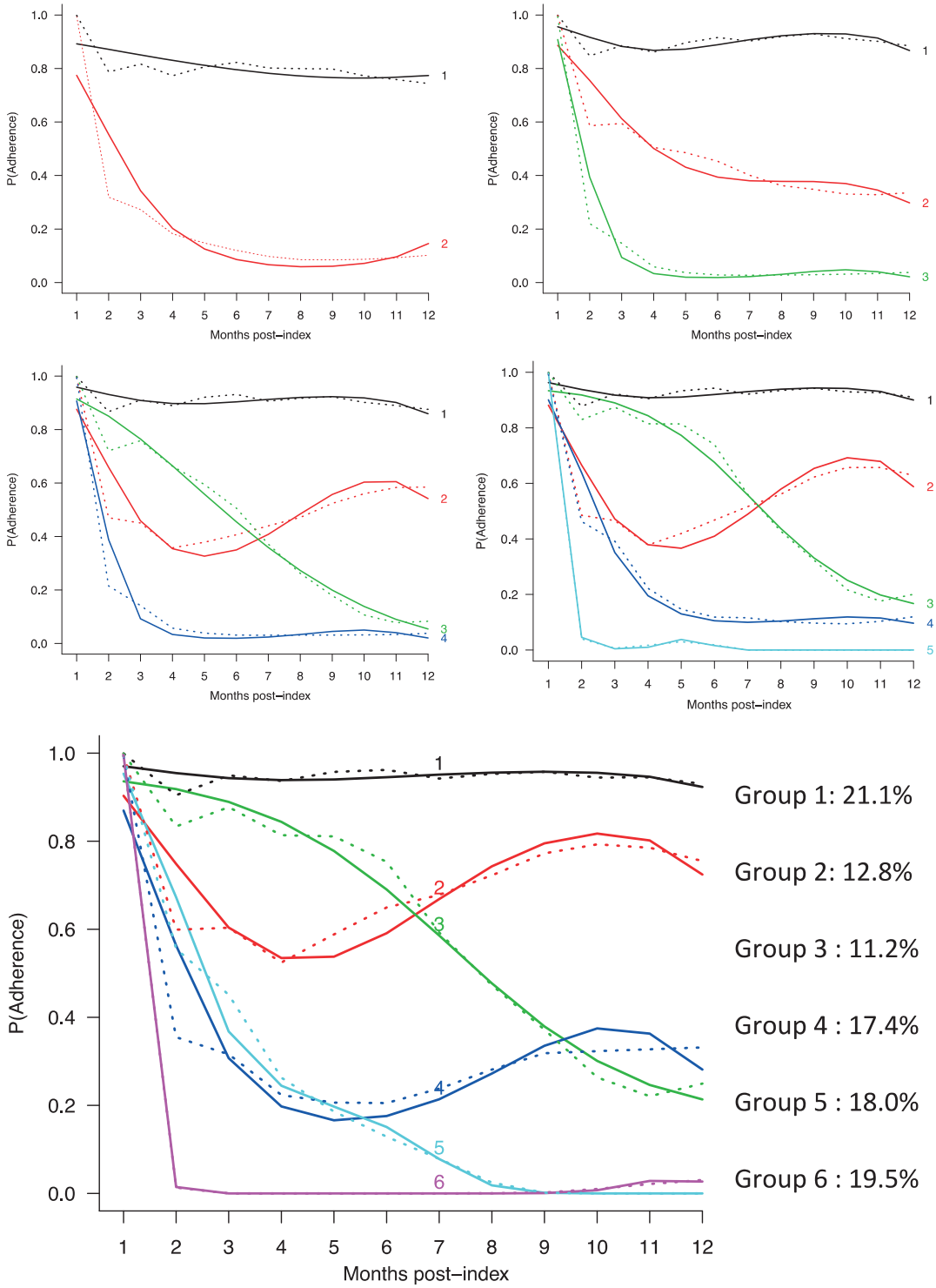

Figure 1. Trajectory models using two to six groups. In each plot, the predicted probability of adherence in each group is plotted with solid lines, and the observed proportion is plotted with dotted lines. For the six-group model, the proportion of patients falling in each group is given to the right

how many groups were included in the model. The largest improvement came from the model that included three trajectory-based adherence groups (Model 6). In this model, there was a net 19.9% (18.1–21.7%) improvement in discrimination compared with the base model. The next highest NRI value came from the model including four trajectory-based groups (Model 8; NRI = 19.6% [17.6–21.6]).

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Table 2. Percent of patients with and without a cardiovascular event assigned to each trajectory group

	Trajectory groupings			PDC groupings		
Adherence group	PDC: mean (SD)	Cardiovascular events	No observed event	PDC: mean (SD)	Cardiovascular events	No observed event
Two-group						
1	0.86 (0.12)	40.9	43.80	0.83 (0.13)	46.8	50.0
2	0.30 (0.19)	59.1	56.20	0.25 (0.15)	53.2	50.0
Three-group						
1	0.93 (0.07)	26.3	29.10	0.92 (0.07)	29.9	33.0
2	0.60 (0.16)	33.1	33.30	0.58 (0.12)	30.5	30.4
3	0.20 (0.12)	40.6	37.60	0.18 (0.09)	39.6	36.6
Four-group						
1	0.93 (0.06)	26.0	28.90	0.95 (0.04)	22.4	25.0
2	0.66 (0.14)	17.1	17.40	0.72 (0.09)	24.4	25.0
3	0.55 (0.15)	15.3	15.00	0.42 (0.08)	20.3	19.5
4	0.20 (0.13)	41.6	38.70	0.15 (0.07)	32.9	30.5
Five-group						
1	0.94 (0.05)	23.2	25.70	0.96 (0.03)	18.0	19.8
2	0.70 (0.13)	15.0	15.60	0.81 (0.06)	18.5	20.2
3	0.66 (0.13)	10.2	10.30	0.57 (0.07)	18.1	18.2
4	0.35 (0.15)	28.5	27.20	0.31 (0.07)	21.0	19.4
5	0.13 (0.08)	23.0	21.20	0.11 (0.04)	24.4	22.4
Six-group						
1	0.95 (0.04)	19.4	21.50	0.97 (0.02)	15.1	16.8
2	0.80 (0.09)	11.4	12.10	0.86 (0.04)	14.7	16.3
3	0.71 (0.12)	10.7	10.90	0.67 (0.06)	16.9	16.9
4	0.51 (0.15)	16.2	15.84	0.46 (0.05)	13.6	13.5
5	0.31 (0.12)	19.0	18.42	0.28 (0.04)	15.3	14.2
6	0.13 (0.08)	23.4	21.18	0.11 (0.04)	24.4	22.3

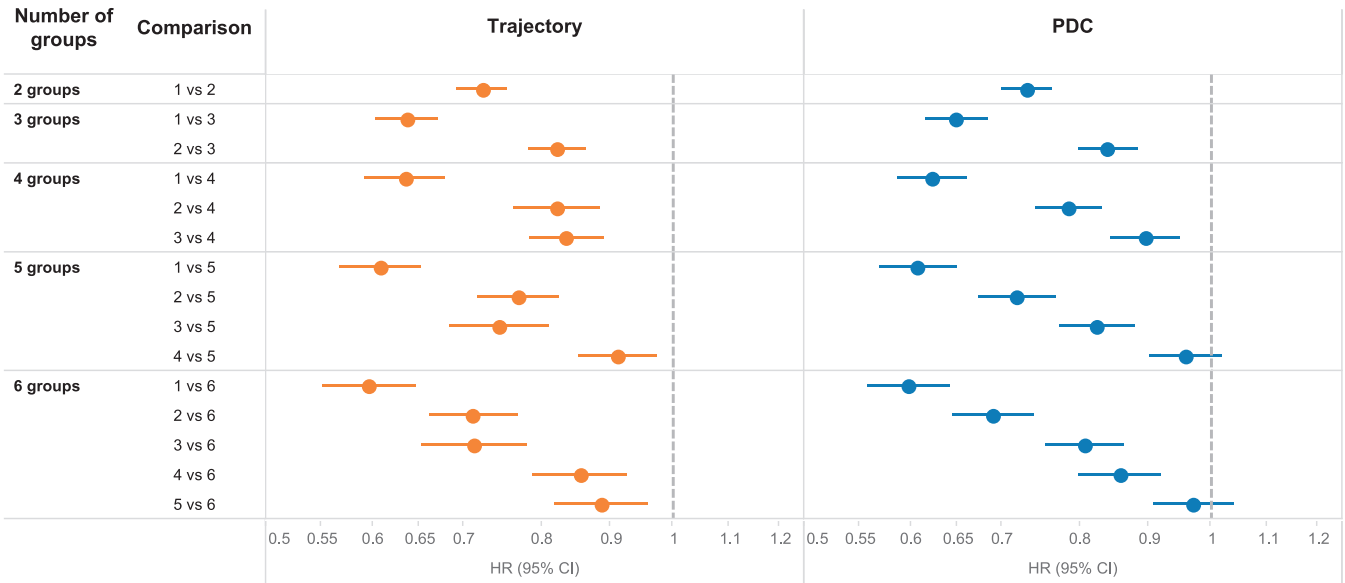

Figure 2. Hazard ratios and 95% confidence intervals for the association between adherence group membership and combined cardiovascular events

When examining reclassification among cases only, the greatest improvement came from the model that included an indicator for PDC > 80% with a net 43.7% of cases reclassified correctly; however, this improvement was offset by the excess 37.1% of controls that were reclassified incorrectly with this model. Only Models 6 and 8, which were the best-performing overall, improved classification of both cases and controls.

DISCUSSION

Among more than half of a million statin initiators, we found that adherence trajectory group was strongly

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Table 3. C-statistics and net reclassification improvement (NRI) for all models evaluated

Model	Adherence measure	C-statistic	NRI	Case NRI	Control NRI
1	Base model	0.771 (0.751, 0.789)	—	—	—
2	+2 groups PDC (split at 80%)	0.772 (0.753, 0.791)	0.066 (0.050, 0.092)	0.437 (0.418, 0.463)	−0.371 (−0.373,−0.368)
3	+2 groups PDC (split at median)	0.773 (0.754, 0.792)	0.072 (0.050, 0.099)	0.072 (0.050, 0.100)	0.000 (−0.004, 0.002)
4	+2 trajectories	0.773 (0.753, 0.791)	0.065 (0.043, 0.086)	0.190 (0.169, 0.211)	−0.125 (−0.127, −0.122)
5	+3 groups PDC	0.773 (0.754, 0.792)	0.178 (0.159, 0.203)	0.246 (0.228, 0.271)	−0.068 (−0.071, −0.065)
6	+3 trajectories	0.773 (0.754, 0.792)	0.199 (0.181, 0.217)	0.158 (0.140, 0.176)	0.041 (0.038, 0.044)
7	+4 groups PDC	0.773 (0.754, 0.792)	0.124 (0.102, 0.145)	0.159 (0.137, 0.181)	−0.035 (−0.038, −0.032)
8	+4 trajectories	0.773 (0.754, 0.792)	0.196 (0.176, 0.216)	0.191 (0.172, 0.212)	0.005 (0.002, 0.008)
9	+5 groups PDC	0.773 (0.754, 0.792)	0.150 (0.130, 0.172)	0.151 (0.131, 0.174)	−0.001 (−0.004, 0.002)
10	+5 trajectories	0.774 (0.754, 0.792)	0.116 (0.098, 0.140)	0.127 (0.110, 0.151)	−0.011 (−0.015, −0.009)
11	+6 groups PDC	0.774 (0.754, 0.792)	0.154 (0.133, 0.179)	0.207 (0.189, 0.232)	−0.053 (−0.056, −0.050)
12	+6 trajectories	0.774 (0.754, 0.792)	0.082 (0.063, 0.102)	0.189 (0.172, 0.210)	−0.108 (−0.111, −0.105)

associated with the likelihood of future cardiovascular events. This association remained across trajectory groupings with differing numbers of groups, but the strongest effects were observed when using five or six trajectory groups and comparing the least adherent trajectory with the most adherent. HRs comparing the most extreme PDC groups were similar, indicating that trajectories and PDC capture similar risk groups at the ends of the adherence spectrum.

However, while the association between adherence group and risk of cardiovascular event was ordered across all PDC groups, the trajectory groups did not exhibit this behavior. Specifically, when using five trajectory groups, patients in trajectory 3 had lower rates of events than patients in trajectory 2, who had better overall adherence. Because the characteristics of patients in these groups were similar, other behavioral and clinical differences not measured in this study may be responsible for this risk reversal. In particular, among patients with moderate adherence, trajectory groupings may have captured empirical patterns of behavior that did not necessarily correspond to ordinal categories of adherence. PDC groups, in contrast, are based on arbitrary cutpoints of medication coverage, which ensure ordinality, but may fail to identify distinct patient behaviors.

Evaluating the improvement in prediction of cardiovascular events achieved by adding adherence measures to the model, C-statistics were essentially identical across models, but NRI values demonstrated improved prediction over the base model for both case and control patients in two models: those using three or four adherence trajectory groups. The improved discrimination observed from NRIs but not from C-statistics is likely due to the fact that the base model already contained several strong predictors of cardiovascular events, and the C-statistic is known to be insensitive to subtle improvements in an already accurate model.[23] Collectively, these results indicate that adherence trajectories discriminate between patients with and without clinical events as well as and in some cases better than PDC-based adherence categories, but neither adherence measure greatly improved the prediction of events.

Although we are unaware of any prior literature describing the association between adherence trajectories and clinical outcomes, there is a large literature on other adherence metrics. Specifically, PDC and medication possession ratio have generally been favored approaches, but nearly all available metrics have been shown to perform similarly across several disease areas.[10,11] There is also abundant research on choosing an "optimal" PDC cutpoint for distinguishing between poor and good adherers; this cutpoint varies somewhat across medications, but a threshold of 80% has generally been found to perform acceptably.[12,26–31] However, this approach to classifying medication adherence assumes that there are just two relevant classes of patients: adherers and nonadherers.

Trajectory groups may ultimately be stronger predictors of clinical events because they additionally distinguish among different types of nonadherence behavior, rather than simply quantifying adherence level. The trajectory curves estimated in this study are very similar to those estimated previously in statin initiators, and this classification of unique behaviors may be more relevant for targeting interventions to patients with specific adherence difficulties. For example, patients who use medication sporadically over a long period may require a different intervention than patients who adhere well for a short period, but eventually become nonpersistent. PDC and related measures cannot distinguish between these groups of patients. However, further research is needed to investigate whether the trajectories observed in this study are generalizable to other chronic disease medications.

When employing trajectory models, investigators must choose the number of groups to use. The Bayesian information criterion (BIC) has been the most

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popular metric for choosing the optimal trajectory model, with a lower BIC preferred.[32,20] However, in large datasets, BIC can nearly always be decreased through the addition of more groups. We chose to limit the number of groups to no more than six to ensure that estimated adherence trajectories were interpretable. In any specific analysis, the optimal number of groups should be decided first by how groups will be used, for example, for targeting adherence interventions, and second by statistical considerations such as BIC. If outcome information is available, investigators may also explore trajectory associations with outcome, as we have done in this study.

One limitation of our study is the temporal distance between observations of adherence and subsequent clinical events. It is likely that nonadherence to statins has a greater impact on the likelihood of a cardiovascular event occurring concurrently or shortly after a patient becomes nonadherent. Similarly, the cardiovascular events observed in our study were likely affected by patients' adherence behaviors during the period of outcome assessment, which could have changed from those observed during the adherence assessment period. However, in order to ensure that all outcomes occurred after assessment of adherence, it was necessary to separate the measurements into these two distinct time periods. Additionally, as our look-back period for assessment of covariates and prior statin use was limited to 1 year prior to statin initiation, some misclassifications of covariates and new user status are inevitable. However, these covariates still predicted future cardiovascular events well. Finally, our study evaluated adherence for just 12 months after initiation; future research should investigate patterns of adherence over longer periods.

Based on the findings of this study, we conclude that adherence trajectories are strongly associated with risk of cardiovascular events, but they add little to the prediction of events. Because trajectory models have also previously been shown to more accurately summarize adherence compared with PDC, they may provide better control for potential confounding by health-seeking behavior in studies of the comparative effectiveness of medications and improved prediction of future adherence by better summarizing past adherence. Clinically, trajectories may provide a better method for targeting adherence interventions to groups of patients most likely to benefit. Prediction of adherence trajectory from baseline data remains challenging,[13] but timely interventions may be able to be deployed if a patient's likely trajectory group can be identified quickly after initiation of medication. Although further research is needed to identify which adherence interventions are most effective in each trajectory group, trajectory models are a promising methodology that could allow providers and payers with access to pharmacy claims to deploy interventions tailored to the specific type of nonadherence behavior exhibited by each patient.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Groupings based on patterns of statin filling behaviors were strongly associated with subsequent cardiovascular events.
- Adherence trajectories predicted future clinical endpoints as well as better than categories of adherence based on the PDC.
- Summarizing adherence with group-based trajectory models provides a more nuanced summary of adherence behaviors, particularly among patients with moderate adherence and may be useful in targeting adherence interventions or adjusting for adherence behavior in comparative effectiveness studies.

ETHICS STATEMENT

This study was approved by the Brigham and Women's Hospital Institutional Review Board.

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