Long-term Persistence in Use of Statin Therapy in Elderly Patients

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Context  Knowledge of long-term persistence with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy is limited because previous studies have observed patients for short periods of time, in closely monitored clinical trials, or in other unrepresentative settings.

Objective  To describe the patterns and predictors of long-term persistence with statin therapy in an elderly US population.

Design, Setting, and Patients  Retrospective cohort study including 34501 enrollees in the New Jersey Medicaid and Pharmaceutical Assistance to the Aged and Disabled programs who were 65 years of age and older, initiated statin treatment between 1990 and 1998, and who were followed up until death, disenrollment, or December 31, 1999.

Main Outcome Measures  Proportion of days covered (PDC) by a statin in each quarter during the first year of therapy and every 6 months thereafter; predictors of suboptimal persistence during each interval (PDC < 80%) were identified using generalized linear models for repeated measures.

Results  The mean PDC was 79% in the first 3 months of treatment, 56% in the second quarter, and 42% after 120 months. Only 1 patient in 4 maintained a PDC of at least 80% after 5 years. The proportion of patients with a PDC less than 80% increased in a log-linear manner, comprising 40%, 61%, and 68% of the cohort after 3, 12, and 120 months, respectively. Independent predictors of poor long-term persistence included nonwhite race, lower income, older age, less cardiovascular morbidity at initiation of therapy, depression, dementia, and occurrence of coronary heart disease events after starting treatment. Patients who initiated therapy between 1996-1998 were 21% to 25% more likely to have a PDC of at least 80% than those who started in 1990.

Conclusions  Persistence with statin therapy in older patients declines substantially over time, with the greatest drop occurring in the first 6 months of treatment. Despite slightly better persistence among patients who began treatment in recent years, long-term use remains low. Interventions are needed early in treatment and among high-risk groups, including those who experience coronary heart disease events after initiating treatment.

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See also pp 462 and 495.
nicians and policymakers because they fail to reveal changes in statin use over time. Targeting persistence-enhancing interventions so that they have the most leverage and potential benefit will require knowledge of the time during therapy when discontinuation is most likely, and which patient subgroups are at highest risk. In addition, long-term persistence rates are necessary to estimate the population-level costs and benefits of statins in actual practice.

To address these issues, we used a repeated measures approach to assess intensity and predictors of statin use among a large cohort of elderly patients for up to 10 years after treatment initiation. Our specific objectives were (1) to describe long-term trends in statin use, including changes over time; (2) to identify patient characteristics that predict poor long-term persistence; and (3) to determine whether the growing evidence in support of statin use has improved persistence over time.

**METHODS**

**Patients**

We conducted a retrospective cohort study covering the period 1990-1999 among enrollees of the New Jersey state Medicaid or Pharmaceutical Assistance to the Aged and Disabled (PAAD) programs who were 65 years of age and older and initiated therapy with a statin (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, or simvastatin) between 1990 and 1998. To protect the confidentiality of program participants, all personal identifiers were removed prior to data analysis. Institutional review board approval was obtained for this research. To be eligible for Medicaid during this period required an annual income below the federal poverty level; PAAD provided pharmacy benefits to a less indigent population, with income ceilings over 200% of the federal poverty level. New Jersey Medicaid had no deductible, co-payment, or maximum benefit for drugs; the PAAD program had no deductible or maximum benefit, but required a $5 co-payment for each prescription filled. Neither program had any formulary restrictions.

Data came from a computerized database of linked pharmacy, physician, hospital, and nursing home claims. Medicaid and PAAD data were available for 1989 through 1999; Medicare data for the same population were available for 1989 through 1998. The date of a patient’s first pharmacy claim for any statin between January 2, 1990, and December 31, 1998, was defined as that subject’s index date. We restricted our analysis to new statin users by including only those enrollees who filled at least 1 prescription for any drug, but no statin prescriptions, during 3 consecutive 6-month intervals prior to the index date. To ensure complete ascertainment of medical and nursing home services, we also required at least 1 claim for any non-drug clinical service during each of these 3 preindex intervals.

Individuals were followed up from the index date until their death, program disenrollment, or December 31, 1999, whichever occurred first. Statin use was measured quarterly during the first year and at 6-month intervals thereafter. Since most elderly patients fill prescriptions for multiple medications,23 we assumed patients had disenrolled from their payer’s program if they filled no prescriptions for any drug in 2 consecutive 6-month periods. If this occurred, statin use was not recorded for these or any subsequent intervals. We tested the sensitivity of results to this assumption by using thresholds of 6 months and 24 months without a prescription claim.

**Outcome Measures**

We use the term “adherence” to represent the degree of prescription-filling in a given interval, and “persistence” to represent the duration of time over which a patient continued to fill statin prescriptions. The quantity dispensed and number of days supplied from each filled prescription were used to calculate the proportion of days on which a patient had a statin available in each interval (proportion of days covered [PDC]). We then divided the cohort into 3 groups at each interval: adherent individuals were defined as those with a PDC of at least 80% in a given interval. Partially adherent individuals were those having a PDC of 20% to 79%; those with a PDC less than 20% were considered nonadherent. We considered partial adherence or nonadherence in a given interval to be signs of suboptimal persistence. Although the amount of clinical benefit achieved at each of these levels of statin use is unknown, we used them to make our results comparable with other studies of medication use.24,25 To determine whether patients who became nonadherent with statins switched to other types of lipid-lowering medications, we also calculated the proportion of these patients who filled at least 1 prescription for a nonstatin lipid-lowering prescription drug in the next interval.

**Potential Predictors of Suboptimal Persistence**

We studied several demographic and clinical characteristics available to a primary care physician when therapy is initiated to identify predictors of suboptimal persistence. Our selection of potential predictors was also informed by previous studies of chronic medication use in elderly patients.19,20,26,27 Demographic variables included age, sex, race, and prescription program (Medicaid or PAAD). Because individuals could not be dually eligible for Medicaid and PAAD prescription coverage, prescription program was a proxy for socioeconomic status. Clinical characteristics were identified based on hospital and outpatient diagnoses, medical procedures, and filled prescriptions during the 365 days prior to the index date. Of particular interest was the influence of pretreatment and posttreatment occurrences of CHD. We categorized patients with evidence of pretreatment CHD into 3 groups: evidence of angina or coronary angiography (CHD group 1); evidence of coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), or chronic CHD (CHD group 2); and evidence of acute MI (CHD group 3). Patients who met the criteria for more than 1 group were assigned to the most severe category. We assessed the influence on persistence of posttreatment CHD occurrences by creating time-
varying covariates for events indicating group 2 and group 3 CHD, in the 12 months preceding a given 6-month interval. Other comorbid conditions assessed in the year prior to therapy included history of stroke, hypertension, congestive heart failure (CHF), diabetes, depression, and dementia.

Health services utilization variables were also based on the year prior to the start of statin therapy and included the frequency of hospitalizations and outpatient physician visits, number of different medications prescribed, Charlson comorbidity score, and residency in a long-term care facility on the index date. To test the hypothesis that persistence may have been better among patients who began therapy after publication of the major statin trials, we divided the cohort into groups based on their index year and then compared persistence during the follow-up period using 1990 as the referent year.

Statistical Methods

The mean and median PDC and the proportion of patients classified as adherent, partially adherent, and nonadherent were calculated for each interval. To identify significant predictors of suboptimal persistence over time, we used generalized linear models for repeated measures to estimate the probability that a subject had less than 80% PDC in each interval. The decline in persistence over time (in months) was assumed to be linear on the log scale, based on comparisons of linear, quadratic, and log-linear univariate models.

Potential predictors of suboptimal persistence were considered statistically significant at the P<.05 level. The final multivariate model was adjusted for time since the index date and for all the characteristics listed above. All statistical procedures were performed using SAS version 8.2.31

RESULTS

Population Characteristics

A total of 34,501 new statin users met our inclusion criteria. Baseline characteristics of the study population are shown in Table 1. Most of the patients were white women, with an average age of 74 years when statin treatment was initiated. Two thirds of the population were enrollees in the PAAD program; the remainder received their drug benefits from Medicaid. Most patients began treatment with simvastatin or lovastatin.

When classified according to the presence of CHD in the year prior to index, 22% of patients had evidence of angina or coronary angiography in the baseline year (group 1); another 15% had a PTCA, CABG, or treatment for chronic CHD (group 2); 7% experienced an acute myocardial infarction (MI) (group 3); and 55% had none of these markers of CHD. During the follow-up period, group 2 and group 3 CHD events occurred in 23% and 10% of patients, respectively. Hypertension was the most prevalent comorbid condition, followed by CHF, diabetes, depression, dementia, and stroke. Twenty-three percent of the cohort died during the follow-up period.

Patterns of Use Over Time

The mean, median, and interquartile range for the PDC observed at each interval over the 10-year period are shown in Figure 1. Statin use declined sharply and early after initiation of therapy, from a mean PDC of 79% in the first 3 months, to 56% after 6 months, and 50% after 12 months. In subsequent years, the mean PDC continued to decline gradually, to a low of 35% after 60 months, but then increased slightly to 42% after 120 months. The median PDC declined much more rapidly than the mean, from 91% after 3 months to 0 at 54 months. Median persistence remained 0 until 102 months, when it began to increase slightly among the relatively small number of remaining patients. These results were robust to changes in the number of inactive months required for a subject to be considered disenrolled from the payer program.

The proportion of patients who were adherent with statin therapy was 60%, 43%, 26%, and 32% after 3, 6, 60, and 120 months, respectively (Figure 2). Virtually none of the cohort were defined as nonadherent during the first 3 months of therapy (because initial supplies were typically 30-90 days). However, nonadherent patients comprised 29% of the population at 6 months and 56% at 60 months, after which the proportion remained approximately constant.

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constant until the final 2 years of follow-up when persistence improved slightly. A large proportion of patients were partially adherent early on, but this group narrowed over time, comprising 40%, 29%, and 18% of the cohort after 3, 6, and 60 months, respectively, with most of these patients transitioning into the nonadherent group. Of those who became nonadherent with statin therapy, only 4% filled a prescription for a non-statin lipid-lowering medication in the next interval, and fewer than 1% had a PDC of at least 80% with that medication. Thus, very few patients could have been misclassified as nonadherent due to switching from statins to other lipid-lowering drugs.

Predictors of Suboptimal Persistence

Results of the multivariate model are shown in Table 2. Long-term use was especially low for patients of black and other nonwhite races, regardless of socioeconomic status, as well as for recipients of Medicaid, regardless of race. After adjusting for all other characteristics studied, black Medicaid recipients had 2.7 times the odds of suboptimal persistence compared with white PAAD recipients. In addition, patients 75 years of age and older had 19% greater odds of poor long-term persistence. Patients treated for depression or dementia were more likely to have suboptimal persistence, while the opposite was true for those with hypertension, stroke, CHF, or diabetes. The odds of suboptimal persistence were slightly higher among patients who were hospitalized in the year prior to initiating therapy and among those with the greatest number of other prescribed medications. Patients who resided in a nursing home were significantly more likely to remain on their prescribed regimen.

Overall, more severe CHD was associated with greater use of statins. Patients with group 1, group 2, and group 3 evidence of CHD were 14%, 27%, and 41% less likely, respectively, to have suboptimal persistence, compared with patients without CHD. However, those who experienced an acute MI had 20% greater odds of suboptimal persistence in the year after the event, compared with those who did not have any CHD event. A similar but smaller effect was observed among patients who experienced a group 2 CHD event during follow-up.

Compared with those who began statin therapy in 1990, patients who started between 1992 and 1993 were about 15% more likely to reduce or omit therapy during the follow-up period. However, patients who initiated therapy more recently (1996-1998) were 21% to 25% less likely to stop or reduce their statin use.

COMMENT

Despite burgeoning evidence of the capacity of lipid-lowering therapy to reduce cardiovascular morbidity and mortality, these findings indicate that their actual use in typical populations of older patients is likely to substantially undercut this potential. A better understanding of the magnitude and predictors of long-term persistence with statins has implications for the approach to managing individual patients, as well as the design and evaluation of population-level cardiovascular risk reduction programs. To our knowledge, this is the first study to observe statin use in routine care settings for a follow-up period comparable to that of the pivotal statin trials.\(^2-6\) Because our cohort was large and typical of many older populations in the United States, it can suggest the proportion of patients expected to have suboptimal persistence with statin therapy at a given point in time under routine conditions. The findings also identify several previously unstudied patient characteristics that can be used to predict poor persistence.

We found actual persistence to be far less than that reported in trials, where 5-year cumulative discontinuation rates ranged from just 6% to 30%.\(^2-6\) By contrast, we found that only 26% of patients were still taking their regimens at a high level after 5 years. This finding extends previous works by our group and by investigators in Australia, who found a 1-year mean of 64% of days with statin available\(^9\) and a 1-year discontinuation rate of 60%,\(^20\) respectively. Our results
differ from those of Andrade et al,21 who found a 1-year discontinuation rate of 15% among patients taking lovastatin in 2 health maintenance organizations. We also found lower utilization than other practice-based studies that monitored persistence over extended periods.18,22 Patients in these studies may have remained on their regimens longer because they were relatively younger, healthier, and of higher socioeconomic status, or received dietary counseling and lipid clinic-based disease management. Patients in the latter 2 studies were also informed that their medication use was being monitored, and one study18 relied on patient-reported medication use, which overstates actual use.32

Comparing our findings with studies of other chronic medications in this population, the mean persistence 12 months after an initial statin prescription (50%) was about the same as the rate we found for antihypertensives (43%),23 but lower than for medication for glaucoma (69%)33 or CHF (70%).34 Rudd24 has pooled data from short-term electronic monitoring of therapy for several chronic diseases to estimate the frequency distribution of adherent, partially adherent, and nonadherent patients to be 50% to 60%, 30% to 40%, and 5% to 10%, respectively. Although we observed a similar distribution in the first 3 months of therapy, long-term persistence was substantially worse in our cohort. This may have been because electronic pill containers can serve to increase adherence by raising patients’ awareness of their medication-taking habits.37 In any case, our findings make it clear that for statins, persistence must be assessed over years rather than months to realize its true clinical and public health impact.

The predictors of suboptimal persistence identified here add new information to previous work19 in which we observed lower persistence among the poorest and oldest patients, as well as those who used the greatest number of prescription drugs. Our analysis confirms that these socioeconomic disparities exist in a much larger cohort of statin users and continue for several years after initiation of therapy. We also found significant disparities in persistence among black and other nonwhite races, which is of particular concern because blacks and Mexican-Americans have a higher prevalence of CHD than whites.1 Patients treated for depression were also less likely to persist in statin use, consistent with our recent observation that depressive symptoms correlate with poor persistence with antihypertensive medications.35

Patients with higher levels of baseline CHD persisted better than their healthier counterparts, suggesting that these patients’ perceived cardiovascular risk influenced their medication-taking behavior. A history of stroke, CHF, diabetes, or hypertension also predicted better persistence. By contrast, those who had an MI after starting statin therapy were significantly less likely to continue their statin use following the event, perhaps because they perceived the drug to be ineffective. This finding is alarming given that clinical trials have shown statins to be most effective when used for secondary prevention.36

We observed moderately higher persistence among patients who initiated statin therapy. Figure 2. Proportion of Patients Classified as Adherent, Partially Adherent, and Nonadherent at Each Interval

See Figure 1 for number of patients evaluated at each interval.
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in therapy after the publication of pivotal trials in the mid-1990s. This finding is consistent with those of Jackevicius et al., who reported an increase in prescribing of statins among elderly patients after the publication of the 4S trial. This suggests that the results of major clinical trials may affect patients’ decisions to continue therapy, physicians’ persistence in prescribing therapy, or both. These results should be interpreted in light of some limitations. First, the study cohort consisted of patients 65 years of age and older, most of whom were women with moderate to low incomes. Although this population is representative of many elderly people in the United States, especially those who receive lipid-lowering medications, different results may have been observed in a more affluent cohort or one that included more men. Statin therapy may have been discontinued by the prescriber for clinically appropriate reasons such as adverse drug events, lack of efficacy, or conversion to nonstatin lipid-lowering therapy. However, lipid-lowering therapy is most often lifelong, adverse drug events are rare with the statins, and we found switching from statins to other lipid-lowering medications to be extremely rare in this population. While we could not measure use of statins obtained from physician samples or out-of-state pharmacies, these scenarios are unlikely since this population’s prescriptions were provided free of charge or for a nominal copayment. In settings where patients must pay for much or all of their statin therapy out-of-pocket, it is likely that persistence could be even worse. The poor persistence we observed also cannot be attributed to death or disenrollment from the payer system because we did not calculate adherence for the interval in which death occurred, and we required ongoing use of any medication as evidence of continuous enrollment. The latter requirement may have misclassified a few nonadherent subjects as disenrolled from their program; but to the extent that this occurred, the results presented herein actually underestimate the true statin discontinuation rate.

These data seem to indicate a slight improvement in persistence 9 to 10 years after the earliest members of the cohort began their statin therapy. However, these findings occurred among surviving, continuously enrolled elderly patients, or about one third of patients who initiated therapy in 1990-1991. This may therefore reflect a “survivor effect” among these patients as well as a secular trend toward improved persistence among all patients at the end of the decade after the publication of pivotal statin trials.

Table 2. Association Between Potential Predictors and Suboptimal Persistence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Ln (months of therapy)</td>
<td>1.49 (1.47-1.51)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Demographics Age ≥75 y</td>
<td>1.19 (1.15-1.24)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>1.01 (0.96-1.06)</td>
<td>.72</td>
</tr>
<tr>
<td>Black race</td>
<td>1.67 (1.58-1.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other nonwhite race</td>
<td>1.69 (1.58-1.80)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Medicaid enrollee (vs PAAD)</td>
<td>1.60 (1.53-1.67)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clinical history in baseline year CHD None</td>
<td>1.00</td>
<td>. . .</td>
</tr>
<tr>
<td>Group 1 (angina or coronary angiography)</td>
<td>0.86 (0.82-0.90)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Group 2 (PTCA, CABG, or chronic CHD)</td>
<td>0.73 (0.69-0.77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Group 3 (acute MI)</td>
<td>0.59 (0.54-0.64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.91 (0.86-0.95)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.93 (0.89-0.97)</td>
<td>.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.86 (0.82-0.90)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Depression</td>
<td>1.19 (1.11-1.28)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>1.36 (1.24-1.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.77 (0.67-0.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Charlson score ≥1</td>
<td>1.00 (0.96-1.05)</td>
<td>.88</td>
</tr>
<tr>
<td>Occurrences of CHD Group 2 (past 12 mo)</td>
<td>1.08 (1.03-1.13)</td>
<td>.002</td>
</tr>
<tr>
<td>Group 3 (past 12 mo)</td>
<td>1.20 (1.11-1.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Health services used in baseline year No. of prescription medications &lt;5</td>
<td>1.00</td>
<td>. . .</td>
</tr>
<tr>
<td>5-7</td>
<td>1.01 (0.96-1.07)</td>
<td>.62</td>
</tr>
<tr>
<td>8-10</td>
<td>1.05 (0.99-1.11)</td>
<td>.11</td>
</tr>
<tr>
<td>≥11</td>
<td>1.21 (1.14-1.29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Outpatient physician encounters &lt;9</td>
<td>1.00</td>
<td>. . .</td>
</tr>
<tr>
<td>9-12</td>
<td>0.96 (0.91-1.01)</td>
<td>.15</td>
</tr>
<tr>
<td>13-20</td>
<td>1.00 (0.95-1.05)</td>
<td>.94</td>
</tr>
<tr>
<td>≥21</td>
<td>1.02 (0.96-1.07)</td>
<td>.56</td>
</tr>
<tr>
<td>Hospitalized in baseline year</td>
<td>1.06 (1.01-1.11)</td>
<td>.02</td>
</tr>
<tr>
<td>Nursing home patient on index date</td>
<td>0.45 (0.39-0.51)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Year of statin initiation</td>
<td>1.00</td>
<td>. . .</td>
</tr>
<tr>
<td>1990</td>
<td>1.07 (0.95-1.19)</td>
<td>.26</td>
</tr>
<tr>
<td>1991</td>
<td>1.14 (1.03-1.27)</td>
<td>.01</td>
</tr>
<tr>
<td>1992</td>
<td>1.15 (1.04-1.27)</td>
<td>.009</td>
</tr>
<tr>
<td>1993</td>
<td>1.08 (0.98-1.20)</td>
<td>.13</td>
</tr>
<tr>
<td>1994</td>
<td>0.98 (0.88-1.08)</td>
<td>.63</td>
</tr>
<tr>
<td>1995</td>
<td>0.78 (0.71-0.86)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1996</td>
<td>0.75 (0.68-0.83)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1997</td>
<td>0.79 (0.72-0.86)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Suboptimal persistence was defined as having less than 80% of days with statin available in a given interval. See footnote to Table 1 for expansions of abbreviations.
†Each variable in model was adjusted for other factors in table.
Our findings have important implications for clinicians and other decision makers responsible for the appropriate use of lipid-lowering medications. They make it clear that one cannot assume that long-term persistence in typical settings will approach the levels observed in prospective trials. Accordingly, predictions of population-wide health benefits of statin therapy based on these trials may be overly optimistic given the poor persistence we observed. Recent meta-analyses suggest that the most effective persistence-enhancing interventions for long-term treatments consist of combinations of more convenient care, information, counseling, reminders, reinforcement, and other forms of supervision or attention.20-41 Our findings suggest that such interventions should be initiated early in therapy and targeted to patients most likely to become nonadherent. Given that our cohort faced little other barriers to persistence, these data contribute to the evidence that studies demonstrating clinical benefit also improve persistence of use. Therefore, improving patients’ understanding of their cardiovascular risk, their medication regimen, and the potential benefits of persistence with statin therapy may further enhance persistence. These and other interventions to improve persistence deserve further study.

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REFERENCES

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